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Current Trends in Allergic Reactions:

A MULTIDISCIPLINARY APPROACH TO PATIENT MANAGEMENT

PRESENTED BY:



**NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES OF
THE NATIONAL INSTITUTES OF HEALTH
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**

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Statement of Need

Allergic diseases, including allergic rhinitis, latex allergy, food allergy, drug allergy, insect sting allergy, urticaria, and atopic dermatitis, affect a substantial proportion of the US population, and their incidence is increasing. Some of these reactions can be fatal if untreated or improperly treated, and the most common of all allergic reactions, allergic rhinitis, can contribute to more serious and difficult-to-treat conditions such as otitis media, sinusitis, and asthma. Despite their rising frequency and potentially serious consequences, allergic disorders are commonly unrecognized, and even the cases that are correctly diagnosed are often suboptimally treated. These facts underscore the need for comprehensive contemporary educational activities for healthcare professionals in the identification and management of allergies. This mandate is supported by consultation with leading experts in allergic disease, a review of the current literature, and the results of surveys conducted at prior symposia.

Educational Objectives

After reading this monograph, clinicians should be able to

- Discuss the increasing prevalence of allergic diseases and their impact on patient quality of life
- Describe the pathophysiology of allergic reactions
- Compare and contrast different types of allergic reactions and their presentation, diagnosis, and treatment
- Evaluate treatment options in the management of allergic reactions
- Explain the clinical implications of allergic reactions and treatment for patient care, function, quality of life, and adherence

Target Audience

Allergists/Immunologists, Pulmonologists, General Practitioners, Internists, Pediatricians, Allied Healthcare Professionals, Dermatologists, Otolaryngologists, Emergency Physicians

Educational Method

Current Trends in Allergic Reactions: A Multidisciplinary Approach to Patient Management as published in this *CLINICIAN*® is based, in part, on the proceedings of a conference that was held on February 10-11, 2003 in Bethesda, Maryland.

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CURRENT TRENDS IN ALLERGIC REACTIONS: A MULTIDISCIPLINARY APPROACH TO PATIENT MANAGEMENT

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Dear Colleague:

Over the past few decades, the allergic patient has become an increasingly common presence in physicians' offices, emergency departments, and hospitals across the country. The prevalence of allergic diseases is rising, and their impact on health, productivity, and quality of life is now much more acutely and widely felt.

All allergic conditions are uncomfortable, and some have serious or fatal consequences such as anaphylaxis and asthma. Despite this, they often go unrecognized, and even those that are correctly identified can be a challenge to treat effectively. Fortunately, the vast majority of allergic patients can now be managed safely and effectively by means of allergen avoidance, drug therapy, and/or immunotherapy. Recent research advances have opened the door to new treatments with significant efficacy and tolerability advantages over earlier generations.

The importance of allergic diseases in the clinical practices of both generalists and specialists was the impetus for a conference presented by the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, on February 10 and 11, 2003. The conference participants included allergists, primary care physicians, immunologists, an otolaryngologist, a pharmacist, a nurse practitioner, and a physician assistant. Their focus was on the etiology, diagnosis, prevention, and management of allergic rhinitis (AR); allergies to latex, foods, drugs, and insect stings; urticaria; and atopic dermatitis.

This monograph presents a summary of the expert presentations and faculty discussion at the conference. Reading it and completing the self-assessment test is designated by National Jewish Medical and Research Center as an educational activity with a maximum of 2 category 1 credits toward the AMA Physician's Recognition Award. We hope you will find it to be an informative and useful tool that helps you develop effective, well-tolerated treatment plans for allergic conditions, in partnership with other health professionals, patients, and their families.

Sincerely,



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THE EPIDEMIOLOGY AND ECONOMIC IMPACT OF ALLERGIC DISEASE

Atopy is defined as an inherited tendency to mount an exaggerated immunoglobulin (Ig)E response to common environmental allergens,¹ typically pollen, mold spores, animal dander, dust mites, foods, insect venom, and drugs. Allergic diseases such as allergic rhinitis (AR), atopic dermatitis, and allergic asthma are the clinical expression of the atopic diathesis, reflecting the many dynamic processes of inflammation, tissue injury, and tissue repair triggered by the interaction of IgE with its high-affinity receptor on mast cells and other effector cells.¹ In most places in this monograph we use the term “allergy” to refer to IgE-mediated diseases. However, “allergy” also has a more general meaning—altered reactivity—and certain immune-mediated reactions to food, latex, and drugs that are not mediated by IgE antibody may at times be referred to as “allergy.” We will point out all those circumstances when “allergy” is used in this way.

The Rising Prevalence of Allergic Disease

Allergic disorders are extremely common, and their prevalence has risen steadily over the past several decades, in the United States and in developed countries worldwide.¹⁻⁴ Each year, AR alone affects 10% to 30% of adults and up to 40% of children in the United States,⁵ figures that are particularly alarming given the frequent association of AR with more serious diseases such as asthma, rhinosinusitis, and otitis media. The reasons for the rise in allergy prevalence remain unclear, although several hypotheses have been proposed (see Pathophysiology section for further detail). Allergies and their sequelae place a uniquely high burden on socioeconomically disadvantaged, inner-city, and minority patients, not only in terms of disease incidence and severity but also in terms of the challenges these patients face in avoiding allergens that are endemic in urban environments and the many barriers they must overcome to obtain consistent, individualized, affordable healthcare.

The Costs of Allergic and Related Diseases

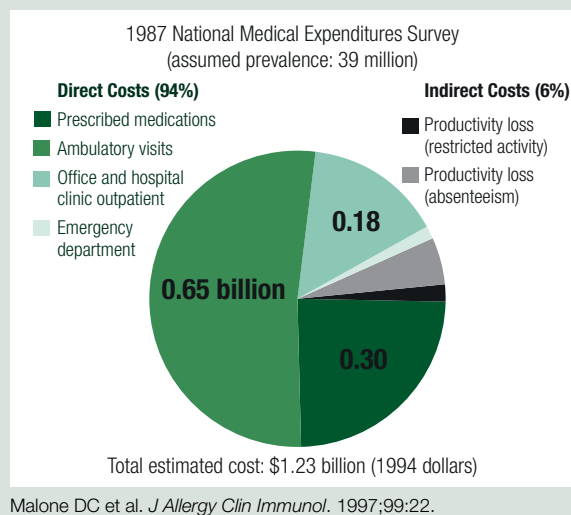
Allergy and its comorbid conditions exact a tremendous economic toll on patients, their employers, and their families. An analysis of data from the National Medical Expenditure Survey indicates that AR alone accounted for \$1.23 billion in 1994 dollars, the vast majority of which (more than \$1.1 billion) was spent on direct costs such as prescription drugs and physician visits (Figure 1).⁶ Asthma, a closely related condition, has been estimated to cost \$12.7 billion annually, more than half of which is in direct medical expenditures.⁷ Approximately \$5.8 billion is spent each year on sinusitis, another common comorbidity of respiratory allergies.⁸ A recent study of adults in a health maintenance organization revealed that those with chronic rhinosinusitis incurred higher healthcare costs than those without, primarily because of nonurgent outpatient visits and pharmacy fills. The overall direct costs of this condition in the United States were extrapolated to be \$4.3 billion.⁹

In fact, these analyses probably understate the actual costs of allergic disease because they do not take into account patients who are never formally diagnosed and simply treat their symptoms with over-the-counter medications. Among patients with AR, for example, it is estimated that only 12% seek medical attention.⁶ Furthermore, many pharmacoeconomic analyses are designed too narrowly to reveal the complete cost-benefit picture. A longitudinal study of data from the National Center for Health Statistics showed that prescription drugs accounted for 30% of all direct asthma-related costs in 1985 but that this figure had risen to 40% by 1994. The overall per-patient costs of treating asthma actually declined slightly over that period, largely because hospital stays had been shortened.¹⁰

The morbidity associated with allergy and related diseases, such as days of school or work lost, reduced productivity at school or work, and reduced ability to perform household chores, also have an indirect economic impact. In one study with almost 2000 patients, 91% reported that their work productivity had been affected by allergy symptoms, 93% reported affected classroom productivity, and 96% reported impaired ability to perform daily activities.¹¹ The impact on quality of life in general is difficult to quantify.

Acknowledging the importance of allergic disorders in the clinical practices of healthcare professionals across many disciplines, a group of specialists in allergy and immunology, primary care, otolaryngology, immunology, pharmacy, and the allied health professions attended a conference presented by the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, on February 10 and 11, 2003, to discuss the current understanding of the etiology, diagnosis, prevention, and management of AR; allergies to latex, foods, drugs, and insect stings; urticaria; and atopic dermatitis. Although asthma is within the spectrum of atopic diseases and is clearly linked to allergy, it is such a large and complex topic that in-depth coverage of it was beyond the scope of the conference. This publication presents a synopsis of the presentations and faculty discussions at this event.

Figure 1
Economic Impact of AR in the United States



THE PATHOPHYSIOLOGY OF ALLERGIC REACTIONS: THE ROLE OF RECEPTORS AND MEDIATORS

Cellular and Molecular Events in the Allergic Response

In atopic individuals, exposure to an antigen (allergen) sets off an immune-mediated cascade of inflammatory events that result in the classic symptoms of allergic disease. The process begins with the first exposure to the antigen, which is broken down into smaller peptides by antigen-presenting cells. The peptides are presented to T cells, which secrete cytokines that induce B cells to produce antigen-specific IgE. These IgE molecules then bind to high-affinity FcεRI receptors on basophils and/or mast cells (Figure 2).¹² This step is called sensitization.¹³

When a sensitized individual next encounters the same allergen, the allergen cross-links the IgE molecules bound to mast cells and basophils in the airways, the gut, and the skin, activating them and causing them to release inflammatory mediators such as histamine, prostaglandins, and leukotrienes.^{1,14} This step, called the immediate hypersensitivity or early-phase reaction, occurs within minutes of reexposure to the allergen and usually resolves within 1 hour.^{1,13}

Histamine is the most well studied of the inflammatory mediators: after allergen exposure, levels are increased in the nasal secretions of patients with AR, the tears of patients with conjunctivitis, the bronchoalveolar fluids of patients with allergic asthma, and the circulation of patients with anaphylaxis. In the upper airway, histamine and other mast cell mediators act on the mucous glands, blood vessels, and nerves to produce the classic early-phase symptoms of nasal congestion, rhinorrhea, itching, and sneezing.^{1,14} In the lower airway, the early-phase effects of these mediators on the secretory glands, blood vessels, and bronchial smooth muscle translate into bronchoconstriction and diminished lung function.^{1,13} In the gut, the response manifests as bloating, cramping, nausea, vomiting, and diarrhea.

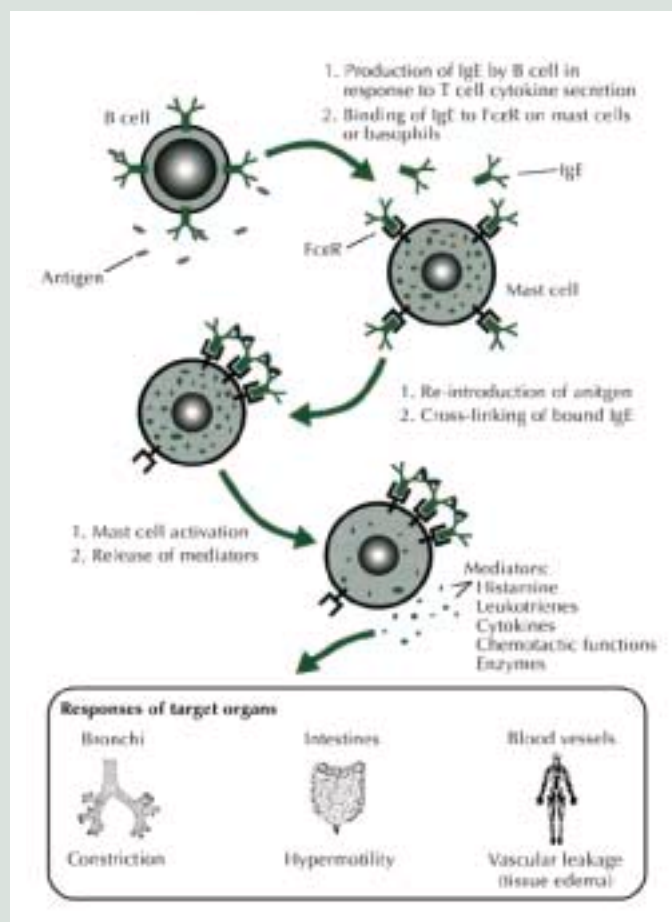
Many patients also have late-phase reactions, which generally begin 2 to 6 hours (or even later for some patients) after allergen exposure and are often more severe and prolonged than the immediate-phase reaction. During this phase, cytokine and chemokine gene induction leads to the accumulation of inflammatory leukocytes, including neutrophils, basophils, eosinophils, and T cells. The consequences in the airway are inflammation, swelling, mucus hypersecretion, and airway hyperresponsiveness. This phase can persist for up to 24 hours before receding.^{1,13,15} Because histamine and other mast cell products also contribute to fibroblast proliferation, collagen synthesis, and chronic tissue eosinophilia, persistent late-phase allergic reactions may play a key role in airway remodeling.¹

Evidence of Immunologic Dysregulation in Atopic Disease

Atopic disease is characterized by abnormal regulation of IgE production, alterations in the distribution of T cell subtypes, abnormal levels of serum and tissue cytokines, and altered frequencies of certain cytokine-producing cells. For example, IgE levels are often abnormally high in patients with allergic asthma and can be correlated with both its prevalence and its severity.¹ However, asthma or atopic dermatitis may also occur in patients without IgE elevations or clinical evidence of allergy. The pathophysiology of these “nonallergic” forms of disease is currently being investigated.^{16,17}

The expression of atopic disease depends on both heritable and environmental factors. Infants are born with the ability to mount cellular immune responses to common allergens in which T-helper cells are biased toward the T_H2 (allergic) cytokine profile. In normal children, this lymphocyte pattern is believed to shift gradually toward T_H1 (nonallergic) responses to inhaled allergens, a process that may be

Figure 2
Cellular and Molecular Events During Allergic Sensitization and the Immediate Hypersensitivity Reaction



Adapted with permission from American Academy of Allergy, Asthma & Immunology. Background. *The Allergy Report. Volume 1: Overview of Allergic Diseases*. Milwaukee, Wis: AAAAI; 2000:5.

related to the child's exposure to certain infectious agents.¹ Children of atopic parents are less able to produce T_H1 cytokines than those of nonatopic parents, and it is now thought that T_H2 -mediated inflammation plays an important role in the development of atopic diseases.¹⁸

Allergic reactions are strictly defined only as those mediated by IgE. Certain disorders, such as allergic contact dermatitis, are not mediated by IgE antibody but may be referred to as "allergy." A single allergic disease may involve more than one immunologic mechanism.

The Mast Cell as a Therapeutic Target

Mast cells are a component of the innate immune system that is "commandeered" by elements of the adaptive immunity system, particularly IgE and the cytokines derived from T_H2 cells, which redirect the functions of the mast cell from antibacterial (protective) immunity to allergic or inflammatory responses.

Several mast cell products have become targets for therapeutic intervention. Histamine has been a target of therapy for decades, particularly of agents that block the H_1 class of histamine receptors. For example, drugs that antagonize H_1 receptors in the nasal mucous glands and vasculature are highly effective in the control of early-phase itching, nasal drainage, sneezing, and vasodilation.¹⁴ More recently, the cysteinyl leukotrienes have been targeted with agents that suppress their synthesis (zileuton) or block their receptors (montelukast and zafirlukast). Because the cysteinyl leukotrienes promote vasodilation, vascular permeability, airway smooth muscle constriction, and lower-airway mucus secretion, leukotriene modifiers may be effective for some patients with asthma; however, they are less effective for those with AR.¹⁴ Cysteinyl leukotrienes bind to 2 types of receptors, the CysLT1 and CysLT2, but most of their biological effects are mediated by stimulation of the CysLT1 type.¹⁹

Attempts to control allergy symptoms by interfering with other proinflammatory mediators produced by mast cells and T_H2 lymphocytes have met with limited success to date. Neither neutralization of interleukin (IL)-4 with a soluble receptor nor recombinant monoclonal antibodies against IL-5 have shown appreciable efficacy in controlling the symptoms of AR or asthma, despite the important role of these cytokines in T_H2 pathways.²⁰ Recombinant human IL-12, an anti-inflammatory cytokine, has shown a similar lack of efficacy in allergic asthma, in addition to serious adverse effects.²¹ These disappointing outcomes probably reflect the many parallel and overlapping pathways that contribute to the allergic/inflammatory response. These redundancies mean that targeting a single mediator or receptor is unlikely to suppress all allergic symptoms effectively, especially if it plays a role only in a distal or late stage of the inflammatory cascade.

Why Is Allergic Disease Becoming More Prevalent?

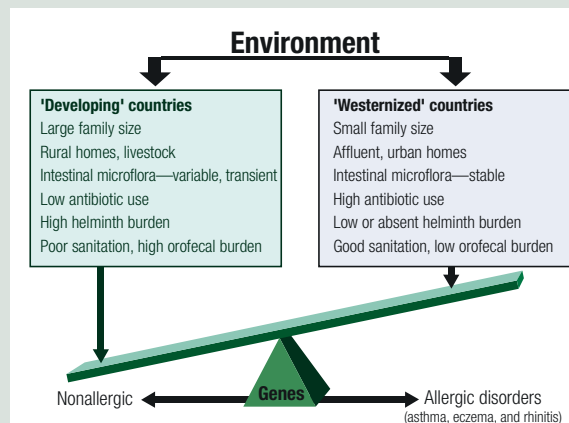
A number of theories have been proposed to explain the rising prevalence of allergic disease in the developed world. One possibility is increased exposure to dust mites and other indoor allergens due to both poor ventilation in modern buildings and a growing tendency for people and their pets

to spend more time indoors. Another possibility is increased exposure to environmental pollutants such as automobile exhaust, diesel particulates, and tobacco smoke. Indeed, studies have indicated that exposure to diesel exhaust particles enhances IgE production and induces histamine release.²² Urban or "westernized" dietary and lifestyle factors may also play a role.^{1,3}

An alternate theory, described as the "hygiene hypothesis," proposes that patterns of immune reactivity are being altered by medical and public-health interventions that reduce exposure to infections or bacterial components such as endotoxin in early childhood (eg, improved sanitation and the widespread use of vaccines and broad-spectrum antibiotics).^{1,23} Initially, it was thought that this reduced exposure drove the immature immune system to develop along T_H2 rather than T_H1 pathways, favoring a tendency toward allergic reactivity.¹⁸ This concept was supported by the observation that children living in rural environments, with large families and limited sanitation, are less likely to have allergies than are children living in urban, affluent settings, with smaller families, good sanitation, and avoidance of infectious agents, particularly intestinal parasites (Figure 3).^{1,18} A recent study confirmed that levels of endotoxin in children's mattresses are inversely correlated with the incidence of allergies, atopic asthma, and atopic sensitization, as well as with leukocyte production of anti-inflammatory cytokines such as IL-10.^{24,25}

The mechanisms by which infections or endotoxin exposure might reduce atopic disease are not well understood.^{23,24} The idea that a reduced microbial burden favors T_H2 responses over T_H1 responses is contradicted by the facts that T_H1 -driven autoimmune diseases are becoming more prevalent and that certain infectious agents such as helminths actually skew cytokine profiles toward a T_H2 pattern.²⁵ Furthermore, allergic and autoimmune diseases often coexist in the same patient.²³ The current view is that persistent challenges to the immune system enhance the production of regulatory cells that inhibit both T_H1 and T_H2 responses.²³ Avoiding infectious agents is thought to undermine this robust anti-inflammatory response, raising the risk of both T_H1 - and T_H2 -mediated diseases.²⁵

Figure 3
The Hygiene Hypothesis



In summary, recent insights into the immunologic pathophysiology underlying allergic disease have permitted the development of therapies targeted to specific elements in the inflammatory cascade. However, much remains to be learned about why the rates of atopic disease are rising so dramatically and whether medical interventions can alter their natural history in clinically useful ways.

OVERVIEW: DIAGNOSIS AND MANAGEMENT OF ALLERGIC REACTIONS

Diagnosis of Allergic Disease: Guidelines and Clinical Pearls

The vast majority of allergic diseases are correctly diagnosed on the basis of a brief history and physical examination. Skin and serologic testing are mainly used to confirm the suspected diagnosis; positive results on these tests are not meaningful unless they are accompanied by clinically significant symptoms. Levels of total serum IgE are elevated in allergic patients, particularly those with atopic dermatitis.²⁶ In addition to measuring total serum IgE, IgE antibody to specific allergens is often measured either via skin-prick test or by measuring levels in the blood. Measuring allergen-specific IgE is useful to verify the diagnosis, to reveal unsuspected sensitivities, and to guide immunotherapy. Blood work does not show the presence of mast cells (if it does, mast cell leukemia should be suspected), and the presence of basophils is not diagnostic of allergy. In contrast, circulating eosinophils may be elevated in allergic disease.²⁶

An important diagnostic clue in the patient's history is the time lag between exposure to the suspected allergen and the emergence of symptoms. For example, ocular symptoms experienced immediately after allergen exposure point to seasonal allergic conjunctivitis or chemosis, whereas those occurring days afterward are more likely to indicate perennial allergic conjunctivitis or dermatoconjunctivitis.

Differential Diagnosis

In the eye, the most common symptoms of allergic disease are itching, watering, and redness. Soreness, swelling, and stinging also occur, but they are less common.²⁷ The major differential diagnoses to consider for patients with redness are conjunctivitis, corneal disorders, acute glaucoma, and acute uveitis. Ocular pain and photophobia are not usually features of allergy, instead suggesting other causes such as trauma, infection, corneal inflammation, aphakia, or iritis. Dryness of the eyes is common in older individuals but may occur at any age. It is not typically a sign of allergic disease; rather, it is often attributable to a dry environment, local ocular disease, systemic disorders such as Sjögren's disease, or drug adverse effects (eg, atropinelike agents).

For patients presenting with angioedema, the differential diagnosis includes cellulitis, edematous states, trauma, or fasciitis. Elements of the history that help pinpoint the diagnosis include the concomitant presence of urticaria, pruritus, gastrointestinal symptoms, or anaphylaxis. Patients should be asked about any apparent triggers of the symptoms and the use of any medications associated with allergic reactions (eg, beta-lactam antibiotics). Clinical

experience indicates that reactions to cyclooxygenase inhibitors and angiotensin-converting-enzyme inhibitors do not involve pruritus, and urticaria is not commonly reported.

Among patients presenting with acute otitis media, the etiology is usually infectious, although allergy, eustachian tube obstruction, and host-defense deficiencies play roles in some cases. Allergy and infections are the 2 most common causes of rhinitis and other nasal symptoms. The differential diagnosis of these conditions is summarized in Table 1.

Allergy also plays a significant part in the pathogenesis of sinusitis—in fact, they coexist so often that they are commonly described as rhinosinusitis.^{8,28} Nasal discharge is a common presenting symptom of sinusitis: A greenish color suggests an infectious etiology, whereas opaque or yellow discharge points more to a noninfectious source, particularly if the nasal smear shows predominantly eosinophils and few neutrophils. Cough is another common feature of sinusitis (especially in children), although it can also represent asthma or a wide variety of other conditions. Other accompanying symptoms that suggest sinusitis include headache, fever, facial pain or swelling, halitosis, maxillary toothache, purulent or colored nasal secretions, and a poor response to decongestants. Asthma, intolerance to aspirin, and chronic rhinosinusitis with associated nasal polyps—the so-called ASA triad—are frequently seen together in patients consulting allergists.^{29,30}

Table 1
Differential Diagnosis of Nasal Symptoms

Pathophysiologic Category	Disorders
Allergic	Seasonal AR (typically pollens) Perennial AR (typically dust mites and molds)
Physiologic	Idiopathic (vasomotor rhinitis) Rhinitis medicamentosa (including cocaine abuse) Medications (reserpine, guanethidine, prazosin) Psychological (anger, sexual arousal)
Hormonal	Pregnancy Hypothyroidism
Mechanical	Polyps Tumors Deviated septum Hypertrophied turbinates Chronic vasomotor rhinitis Foreign body Central nervous system leak
Chronic inflammatory	Sarcoid Vasculitis
Infectious	Acute viral infection Acute or chronic bacterial infection

Allergen-Avoidance Measures

The management of allergic disease rests on 5 basic elements: trigger avoidance, drug therapy, monitoring, patient education, and immunotherapy. The success of allergen avoidance depends on accurate identification of the culprit antigens, practical advice on how to minimize exposure in the home and workplace, and continued reinforcement and support from the healthcare team. Avoidance is challenging for most patients, especially those sensitive to dust mites or common airborne allergens. Nevertheless, measures that are known to be effective should be encouraged at every office visit, and patients should clearly understand that drug therapy is an adjunct to these measures, not a substitute for them.³¹

Recent evidence suggests that it may even be possible to prevent allergic disease in at-risk children (described as primary prevention). One study enrolled the infants of 291 couples with no pets in which both parents were atopic. The families were randomized prenatally into 2 groups: One implemented environmental measures to reduce prenatal and postnatal allergen exposure, and the other received no intervention. By 1 year of age, respiratory symptoms such as wheezing and use of medication for wheezing were significantly less common in children in the allergen-avoidance group than in those in the control group.³² Similarly, avoidance of food allergens and dust mites in infancy has been shown to reduce the incidence of allergy and eczema significantly in high-risk children by 2 years of age.³³ Later follow-up studies showed sustained effects.³⁴ It should be noted that this type of primary prevention trial is in the early stages, and more information is needed before this approach can be recommended widely. Although sensitization usually follows exposure to high concentrations of allergens, cat allergen may be an exception to the rule; recent studies suggest that under certain circumstances, having dogs or cats in the home may *decrease* the likelihood of sensitization in young children.^{35,36} This paradoxical protective effect raises interesting questions, but the data are too preliminary to drive a change in recommendations at this point. In fact, cats carry certain infectious diseases that pregnant women should avoid, so acquisition of cats should not be advised as a strategy to protect newborns from sensitization.

Pharmacotherapy: General Guidelines

The choice of drug therapy for allergic disease involves a complex set of interacting variables, each of which can influence overall clinical outcome in subtle or pronounced ways. Even what appear to be straightforward criteria for the choice can in fact be quite complex. A drug's efficacy, for example, is not so much a single value as a mosaic of its effects against each individual allergic symptom, which can vary widely; therefore, drug therapy cannot be based on the symptom alone. This was illustrated by a recent study of patients with seasonal AR, in which a nasal corticosteroid was found to be significantly better than a leukotriene modifier in relieving nasal blockage but not significantly better in controlling sneezing, rhinorrhea, or itching.³⁷ In addition to varying across symptoms, efficacy also varies tremendously between patients, probably because of genetic polymorphisms and the heterogeneity of disease pathophysiologies. Likewise, the frequency, severity, and tolerability of side effects show striking interpatient variability.

The Stepwise Approach to AR Management

The Allergic Rhinitis Impact in Asthma (ARIA) guidelines offer a stepwise approach to the drug treatment of AR (Figure 4). The objectives are to provide adequate symptom relief, address comorbidities, and restore acceptable quality of life with drug therapy. Mild, intermittent symptoms may be treated with a nonsedating antihistamine, with or without a decongestant. For moderate or persistent symptoms, an intranasal corticosteroid is added to the choices. Oral corticosteroids may also be needed, although the efficacy of a short course of a systemic corticosteroid has not been demonstrated in published studies.³⁸ To minimize costs and side effects, reducing the number of drugs or their doses may be considered once symptom control has been achieved, especially during seasons or periods when the allergies are not as severe.³⁹

If AR symptoms are resistant to this approach or interfere markedly with the patient's functioning or quality of life, referral to a specialist is recommended for further evaluation of possible triggers, management of comorbidities, and exploration of the possibility of immunotherapy. Because the symptoms of AR last for many years or even a lifetime, the long-term safety, tolerability, and acceptability of each intervention should be considered carefully in consultation with patients and their families.

Pharmacokinetic and pharmacodynamic profiles also guide the choice of drug therapy. For example, in vitro measures such as receptor-binding affinity, protein binding, volume of distribution, and clearance rates can be used to predict the clinical activity of glucocorticoids accurately and are therefore a useful dose-finding tool. With antihistamines, pharmacokinetic parameters such as the route and rate of clearance play an important part in determining the risk of side effects and drug interactions. Fexofenadine and cetirizine are eliminated primarily via renal pathways; hence, renal function determines clearance rate and dose. Conversely, hepatic clearance pathways predominate for loratadine and desloratadine. For these agents, liver function dictates dose, and there is a risk of interactions with foods or drugs that are metabolized by the same hepatic enzymes. Patients may differ considerably in the activity of individual hepatic enzymes, raising the risk of drug accumulation and dose-related adverse events in slow metabolizers. With antihistamines that are cleared by hepatic routes, the risk of adverse effects may be particularly high for patients who are slow metabolizers, because their exposure to the active compound is greater and more prolonged than for normal metabolizers. With desloratadine, for example, approximately 7% of subjects in pharmacokinetic studies (including about 20% of black patients) were found to be slow metabolizers, resulting in a 6-fold increase in exposure to desloratadine. According to the manufacturer, "slow metabolizers may be more susceptible to dose-related adverse events."⁴⁰

Coexisting illnesses must also influence the choice of pharmacotherapy for allergies, and many are absolute or relative contraindications to certain drugs (for example, pseudoephedrine should be used very cautiously by patients with cardiac arrhythmias, coronary heart disease, hypertension, hyperthyroidism, glaucoma, diabetes, or

urinary dysfunction).¹⁵ On the other hand, effective treatment of rhinitis can have synergistic benefits in the management of comorbid disorders such as asthma, sinusitis, and chronic otitis media. In fact, controlling upper-airway inflammation is often a necessary component of treating allergic asthma.⁵

Last, and perhaps most important, any definition of efficacy or tolerability is incomplete without reference to the drug's effects on daily functioning and quality of life—which may be either enhanced by symptom relief or impaired by adverse events. These global measures are among the most important drivers of patient acceptability. The likelihood of adherence to a prescribed regimen is influenced not only by its efficacy and tolerability but also by many other aspects of acceptability, such as the cost, the convenience of purchasing and using it, the frequency and complexity of the dosing schedule, the patient's understanding of how to use the product or delivery device, the taste or smell of the product, and the patient's or parent's attitudes about disease and treatment. Finally, adherence depends greatly on the patient's personal interaction with the healthcare team over the course of the illness.

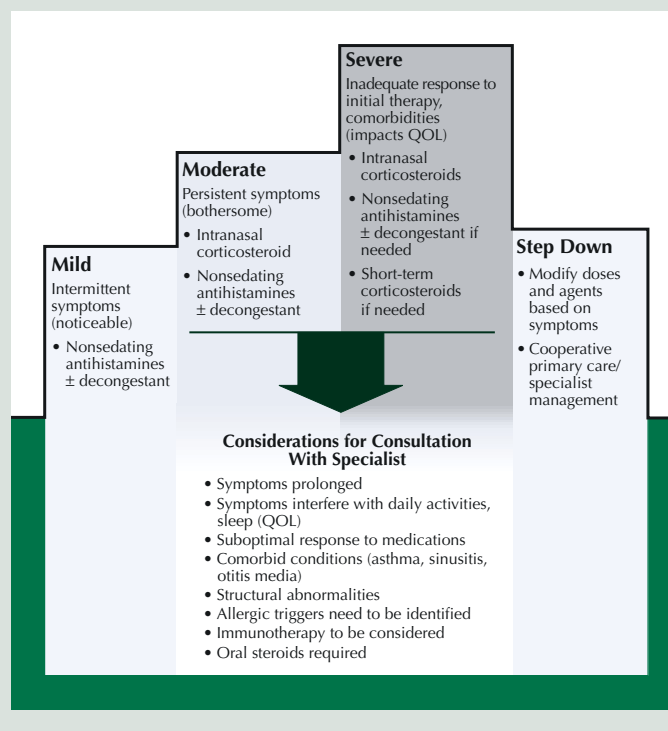
Immunotherapy

Immunotherapy consists of repeated subcutaneous injections of potent standardized extracts of specific allergens, usually starting with 1 to 2 injections per week for up to 1 year, followed by once-monthly injections for at least 3 to 5 years (or longer for some patients). The dose of allergen is increased over time, which gradually raises the patient's tolerance to it, thereby minimizing symptomatic expression of the disease.⁴¹ Immunotherapy has efficacy for treating allergies to insect venom and for treating allergic rhinitis caused by airborne allergens such as pollens, mold spores, house dust mite, and animal danders. Its efficacy in treating asthma is controversial. Currently available allergen preparations have no proven efficacy for allergies to latex or food. Indeed, immunotherapy with food allergen preparations may be unsafe because of the high rate of systemic reactions to allergen injections. The major benefit of immunotherapy is that if it is clinically effective, it may reduce the need for drug therapy. Its mechanism of action remains unclear, but when it is successful, immunotherapy can confer long-term protection even after injections are discontinued.⁴²

Immunotherapy is generally considered for patients with well-defined, clinically relevant allergic triggers that markedly affect quality of life or daily function and who do not attain adequate symptom relief with drug therapy. Because anaphylactic reactions can occur during immunotherapy, this type of therapy must be administered by trained professionals in a facility with direct access to emergency treatment. An optimal maintenance dose in the range of 5 to 20 µg of major allergen per injection correlates with efficacy.⁴² In most cases systemic reactions are rare, and nonallergist medical personnel can administer treatment under the supervision of an allergy/immunology specialist.¹² For patients with birch pollen allergy, specific immunotherapy is more effective than intranasal corticosteroids in reducing lower airway inflammation. In children with AR caused by birch and/or timothy grass, immunotherapy significantly reduces methacholine sensitivity and the subsequent development of asthma.

Figure 4

The Stepwise Approach to AR Management Advocated in the World Health Organization's ARIA Guidelines



The Role of Complementary and Alternative Medicine

The popularity of complementary or alternative medicine (CAM) has grown tremendously in recent years. In fact, allergy is second only to back pain as the most common chronic condition for which people seek alternative therapies.⁴³ In a survey of 300 adults with rhinosinusitis or asthma, almost half reported using CAM during the previous year, and a quarter of these respondents had not used any prescription medication along with their CAM.⁴⁴ The most common forms of CAM are nontraditional medicines such as homeopathic remedies, body manipulation (chiropractic therapy or massage), “energy therapy” (the manipulation of biomagnetic fields), and biologically based therapies such as herbal products and vitamins.

Although a few studies support the use of some types of CAM in the treatment of AR, well-designed scientific research is not plentiful.^{43,45} Despite the lack of evidence, many patients believe that these agents are safe because they are derived from plants. In fact, the chemical composition of flowering and herbal plants is complex, and many are toxic if not used correctly.⁴³ For example, extracts of the Chinese shrub ephedra (*ma huang*) may have modest efficacy in respiratory allergies because they contain alkaloids that promote vasoconstriction and bronchodilation, but ephedra is now known to have potentially serious adverse effects such as vasospasm of the cerebral and coronary arteries, hypertension, tachycardia, and myocardial infarction. Another example is echinacea, a botanical extract that many patients believe to be immunostimulatory. It does

not appear to be effective in allergic disorders, and, ironically, there are now several reports of anaphylaxis associated with it, complete with positive skin tests indicating IgE-mediated reactions.^{46,47}

The manufacturing of CAM agents is largely unregulated; there are no standards to ensure their potency or purity.⁴⁵ However, patients who perceive benefits from these agents are likely to continue using them and will distrust physicians who simply instruct them to discontinue use. Unless the CAM product is clearly dangerous, it is better to initiate a nonjudgmental dialogue about it, monitor the patient's response over time, and provide balanced education and information. If patients derive a sense of self-efficacy and self-reliance from using a harmless nontraditional product together with their prescribed medications, the psychological benefits may have genuine clinical value.

Patient and Family Education

With the current limitations on the length of office visits, few physicians have the time to provide comprehensive education on the natural history of allergic disease or on its triggers, prevention, and treatment. Yet the management of lifelong conditions succeeds only with the participation of motivated patients who are equipped to understand and cope with the daily challenges of their own care. Posters, brochures, and flyers in the waiting room can be helpful, but some patients may not have the reading or English-language skills to interpret them. If possible, the physician's messages should be reinforced by allied health professionals such as nurses or physician assistants, either immediately after the office visit or by telephone. Video- or audiotapes playing in the waiting room can also be a useful adjunct. Even as simple a technique as advising patients where to find the nearest pharmacy can increase the chances that a prescription will be filled and the medicine used appropriately.

The American Academy of Allergy, Asthma and Immunology has a library of patient-centered publications available at <http://www.aaaai.org/patients.stm>, and other valuable consumer information may be obtained from the Food Allergy & Anaphylaxis Network (<http://www.foodallergy.org>), the Allergy & Asthma Network Mothers of Asthmatics (<http://www.aanma.org>), and LungLine® Information Service (<http://www.nationaljewish.org>). Long-term management of allergic conditions works best as a team effort, with the patient viewed as an integral and empowered partner.

FOCUS ON ALLERGIC RHINITIS: TOOLS FOR COMPREHENSIVE MANAGEMENT

Classification of AR

Although AR is traditionally thought of as being either seasonal or perennial, this distinction really applies only to regions of the country with pronounced seasonal weather changes. In other regions, pollens and other airborne allergens are prevalent year-round without much variation. A different classification system has been developed by the World Health Organization in their ARIA guidelines, which classify the disease as being intermittent (less than 4 days per week or less than 4 weeks per year) or persistent (more

than 4 days per week *and* more than 4 weeks per year).³⁹ This system is limited, however, in that the "seasons" of some allergens, such as ragweed, last longer than 4 weeks and are, nonetheless, intermittent.

The severity of the disease is graded in terms of how much the symptoms affect sleep quality, daily functioning, and work or school productivity, as well as the patient's subjective impression of how troublesome they are.³⁸

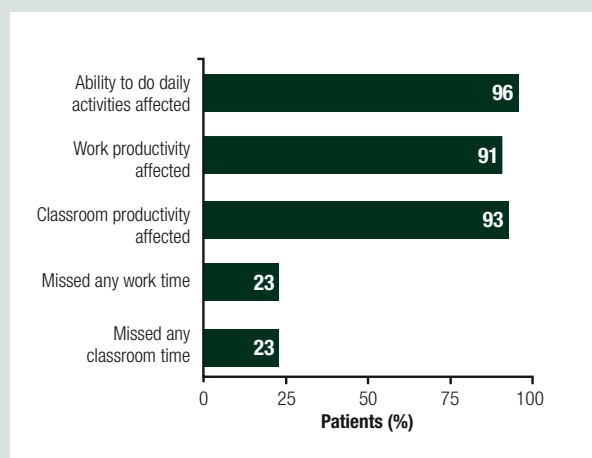
Overall Health Impact of AR

In addition to its physical and emotional impact, AR also impairs overall health because of its many comorbidities. The majority of patients with AR also suffer from associated conditions such as allergic conjunctivitis, otitis media, sinusitis, and asthma. In a Japanese study, for example, otitis media was diagnosed in 21% of children with nasal allergies, compared with just 6% of a control group ($P<.01$). Conversely, among children diagnosed with chronic otitis media, fully half had nasal allergies, compared with just one sixth of the control group ($P<.01$).⁴⁸ In most cases of asthma, AR precedes or accompanies it and is very likely to play an etiologic role. The nasal symptoms of AR may even contribute to orthodontic disturbances: children with nasal congestion or obstruction often become "mouth breathers," which can alter the development of their teeth and jaws over time, leading to disorders such as dental malocclusion.¹⁵

In addition to these comorbidities, numerous studies have documented the adverse impact of AR on quality of life, physical and emotional status, sleep quality, work/school performance, and participation in daily activities (Figure 5).^{11,27,49,50} For example, questionnaire studies of adolescents with allergic rhinoconjunctivitis show that the great majority feel tired, unattractive, irritable, unable to concentrate, and unable to do well in school because of their symptoms.^{27,51}

Figure 5

Percentage of Patients With Moderate to Severe Seasonal AR Who Reported Disease-Related Absenteeism or Impairment in the Workplace or Classroom or in Their Daily Activities Over a 7-Day Period



Adapted with permission from Tanner LA et al. *Am J Managed Care*. 1999;5(suppl):S239.

Allergen Avoidance

Among the most common triggers of AR are grass and tree pollens, molds, dust mites, and animal danders. Avoiding these allergens is a fundamental part of controlling AR, and all patients should be advised on practical measures to protect themselves and their families, such as using air conditioners with special filters and keeping fur-bearing pets out of the bedroom (Table 2). Unfortunately, complete avoidance of airborne allergens is rarely achievable, and most patients need drug therapy.

Pharmacotherapy

A wide variety of topical and oral treatments are available for AR symptoms. Locally applied agents include decongestants, mast cell stabilizers, antihistamines, corticosteroids, and anticholinergics. Systemic agents include decongestants, antihistamines, corticosteroids, anticholinergics, and leukotriene modifiers; of these, antihistamines are the most commonly used in the United States.

Table 2 Environmental Measures to Minimize Allergen Exposure	
Allergen	Recommendations for Reducing Exposure
Animal dander	<ul style="list-style-type: none">Remove animal from house or, at minimum, keep animal out of patient's bedroomSeal (or cover with a filter) air ducts that lead to bedroomInstall room air filters (HEPA type)
Dust mites	<p>Essential:</p> <ul style="list-style-type: none">Reduce indoor humidity to <50%Encase mattress, pillow, and box springs in an allergen-impermeable coverWashing bedding weekly in hot water (≥130° F) <p>Desirable:</p> <ul style="list-style-type: none">Minimize upholstered furnitureRemove carpets from bedroom and from other rooms where they are laid on concrete
Cockroaches	<ul style="list-style-type: none">Do not leave food or garbage exposedUse poison bait or traps
Pollens and outdoor molds	<ul style="list-style-type: none">Use air conditioningLimit exposure during season by staying indoors with windows closed, especially when pollen levels are elevated
Indoor mold	<ul style="list-style-type: none">Reduce indoor humidity to <50%Fix all water leaksClean moldy surfaces

Adapted with permission from American Academy of Allergy, Asthma & Immunology. Asthma. *The Allergy Report. Volume 2: Diseases of the Atopic Diathesis*. Milwaukee, Wis: AAAAI; 2000:52.

Corticosteroids

Intranasal Agents

Highly potent, rapidly metabolized intranasal steroid sprays such as beclomethasone dipropionate, flunisolide, triamcinolone acetonide, budesonide, fluticasone propionate, and mometasone furoate are the most effective agents currently available for preventing itching, sneezing, rhinorrhea, congestion, and cough.⁵ These agents act by reducing inflammatory cell infiltration, decreasing vascular permeability, diminishing the response of mucous glands to cholinergic stimulation, and controlling nasal hyperreactivity.⁵²⁻⁵⁴ Beneficial effects of inhaled corticosteroids have been reported on many of the cells involved in airway inflammation, such as macrophages, T lymphocytes, eosinophils, airway epithelial cells, and mast cells.⁵⁵ Because they may work by entering the nuclei of airway cells and modulating gene transcription,⁵⁵ intranasal corticosteroids may take hours or days to provide significant symptom relief after acute dosing.^{40,56} Many patients require a combination of a nasal steroid and an antihistamine for maximum symptom relief. Patients should be instructed that using topical steroids on a regular basis, even when symptoms are not present, is most effective.⁵²

Oral Agents

Systemic corticosteroids are highly effective anti-inflammatory agents and may be necessary for patients with severe or intractable symptoms.⁵ They have a number of potentially serious side effects, however, such as osteoporosis, glaucoma, and growth retardation in children. For this reason, topical steroids are preferred for the treatment of ongoing allergy, and courses of oral steroids should be kept to a maximum of 3 to 7 days.⁵

Antihistamines

Intranasal Agents

Azelastine is a second-generation antihistamine nasal spray that can significantly decrease allergen-induced sneezing, rhinorrhea, itching, and nasal congestion in patients with seasonal AR.⁵⁷ In a head-to-head comparison in patients with seasonal AR, it was found to be equivalent to oral cetirizine in controlling nasal and ocular symptoms and was in fact superior in terms of patient-rated nasal stuffiness and rhinorrhea. Furthermore, drowsiness was significantly less common with azelastine than with cetirizine.⁵⁸

Oral Agents

Oral antihistamines quickly and effectively relieve itching of the eyes and nose, sneezing, and rhinorrhea, although most have a more modest effect on nasal obstruction or congestion.⁵ The antihistamines vary considerably in their duration of action and their ability to suppress the release of histamine and other inflammatory mediators, which in turn determine the dosing schedule and the degree of symptom relief. In a recent study of antihistamine potency, suppression of the wheal-and-flare response to skin-prick testing with histamine was significantly greater and faster with fexofenadine 180 mg than with loratadine 10 mg.⁵⁹ Head-to-head comparisons have shown that fexofenadine is as effective as cetirizine and that both are more effective than loratadine in controlling seasonal AR symptoms.⁶⁰⁻⁶⁴

The oral antihistamines can be classified according to their potential for adverse events (Table 3).^{65,66} First-generation agents are generally lipophilic and hence can cause psychomotor and cognitive impairment because of their ability to penetrate the blood-brain barrier and their antiserotonin and anticholinergic effects.⁵² By comparison, the newer, or second-generation, antihistamines cause little or no sedation because of their low lipophilicity, their large molecular size, their greater affinity for peripheral H₁ receptors, and their relative lack of affinity for neuroreceptors.⁶⁷ All second-generation agents are preferable to their predecessors for these reasons, but there may be differences even within this class in terms of sedative effects.⁶⁷ Tolerance to sedation does not develop over time,⁶⁶ and the stimulatory effects of decongestants do little to counteract it.

The onset of action of oral antihistamines is generally rapid. Fexofenadine and cetirizine begin to relieve symptoms within 1 hour of administration, and loratadine has a somewhat later onset of action at approximately 3 hours.^{64,65} In general, better therapeutic results are achieved when antihistamines are taken routinely rather than sporadically. Several of the second-generation antihistamines are available in combination with a decongestant, which may be helpful for patients with pronounced nasal congestion and blockage.⁵² It has been suggested that intranasal corticosteroids may be more effective in controlling nasal blockage and discharge, and oral antihistamines may be better at treating nasal itch, sneezing, and eye symptoms.⁶⁸ According to the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology, oral antihistamines are considered first-line therapy in the treatment of AR.⁵

Mast Cell Stabilizers

Intranasal Agents

Mast cell stabilizers, which include intranasal cromolyn sodium and cromolynlike agents, act by stabilizing the membranes of mast cells, inhibiting the release of histamine

and other inflammatory mediators such as prostaglandins and leukotrienes. Modulation of cytokine release also reduces eosinophil and neutrophil counts during the late-phase response. In addition, mast cell stabilizers may suppress the activity of sensory nerve endings. Together, these activities help alleviate both the early- and late-phase symptoms of AR. Cromolyn can be used therapeutically or, preferably, prophylactically in chronic AR to reduce the symptoms of sneezing, itching, and rhinorrhea, although it is less effective against nasal congestion.

An advantage of mast cell stabilizers is their excellent safety record. Their chief disadvantage is a very short duration of action, which necessitates administration several times per day.⁵³ Adherence to a regimen of multiple daily doses may be poor, so the number of doses should be adjusted downward as symptoms abate.

Decongestants

Intranasal Agents

Intranasal decongestants such as phenylephrine and oxymetazoline are available over the counter and are generally more effective than oral decongestants, although their benefits are limited to congestion.⁶⁹ A potential drawback of topical decongestants is that regular use leads to downregulation of alpha-adrenergic receptors, which eventually diminishes their efficacy (tachyphylaxis).^{15,53} A major and often underestimated side effect of these agents is rhinitis medicamentosa, a rebound phenomenon that results in exacerbation of nasal congestion when the agents are used for more than 3 days.⁶⁹ Treatment of rhinitis medicamentosa requires complete, gradual discontinuation of nasal decongestants (which patients may find very difficult) and the possible addition of steroids.⁵³

Oral Agents

Oral decongestants alleviate nasal blockage by promoting vasoconstriction via stimulation of alpha-adrenergic receptors. They improve nasal patency to some degree, but their potential side effects at therapeutic doses include hypertension, restlessness, agitation, tremor, headache, insomnia, urinary obstruction, and changes in cardiac rhythm.⁵² One of the 2 commonly used oral decongestants, phenylpropanolamine, was recently deemed unsafe by the Food and Drug Administration.⁷⁰ The other, pseudoephedrine, remains available. Products containing phenylpropanolamine are no longer sold in stores, but patients may still have them at home and should be advised to discard them.

Anticholinergics

Intranasal Agents

Rhinorrhea due to allergies and other causes can be safely and effectively alleviated with intranasal anticholinergic agents such as ipratropium bromide.⁷¹ In a study of 533 patients with allergic or nonallergic perennial rhinitis, both ipratropium nasal spray and beclomethasone dipropionate nasal spray were superior to placebo in reducing the severity and duration of rhinorrhea, and the combination of the 2 sprays was more effective than either one alone.⁷² However, topical anticholinergics have little effect on postnasal drainage, pruritus, sneezing, or nasal congestion.^{71,72}

Table 3

Proposed Classification System for Oral Antihistamines

Not sedating	Potentially sedating at standard doses	Potentially sedating at higher-than-recommended doses	First-generation antihistamines: sedating at standard doses
Fexofenadine	Cetirizine	Cetirizine	Diphenhydramine [†]
		Loratadine	Cyproheptadine [†]
		Desloratadine	Hydroxyzine [†]
		Mizolastine*	Chlorpheniramine
			Brompheniramine
			Clemastine

*Not available in the US.

[†]Potentially cardiotoxic at overdose.

Howarth PH. *Clin Exp Allergy Rev.* 2002;2:18-25. Casale TB, et al. *J Allergy Clin Immunol.* 2003;111:S835-S842. Simons FER. Antihistamines. In: Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER, eds. *Middletons Allergy Principles and Practice.* St. Louis, Mo: Mosby; 2003:834-869.

Leukotriene Modifiers

Oral Agents

Leukotriene modifiers control allergic symptoms by inhibiting the synthesis of leukotrienes or blocking their receptors. In a double-blind, multicenter, randomized trial of more than 1300 patients with seasonal AR, both a leukotriene modifier (montelukast) and a second-generation antihistamine (loratadine) were found to be significantly superior to placebo in relieving nasal symptoms (Figure 6).⁷³ A recent comprehensive literature review concluded that leukotriene receptor antagonists are not superior to second-generation antihistamines in relieving congestion or other nasal symptoms and that there is not a unique role for leukotriene receptor antagonists in the treatment of AR, whether or not the AR is accompanied by asthma.¹⁴

Effects of Treatment on Patient Functioning and Quality of Life

Effective treatment of allergies not only improves symptoms, it also enhances quality of life for patients and their families. For example, rigorously designed studies have shown that second-generation antihistamines improve quality of life for patients with AR to a statistically and clinically significant degree, as well as alleviating impairments in work and daily activities.^{61,74,75} Quality of life is also significantly better after treatment with an intranasal steroid or a leukotriene modifier.^{76,77}

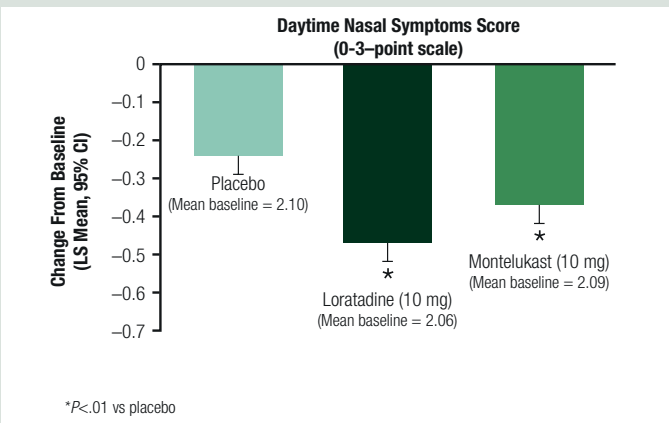
Key Safety and Tolerability Issues

Antihistamines

In selecting allergy medications, it is essential not to compound the adverse impact of the disease itself. This is a major concern with first-generation antihistamines, which can have sedating effects that add to the fatigue and performance impairment associated with allergies. Furthermore, they disrupt normal sleep architecture, which can cause patients to feel unrested even if their nighttime allergy symptoms are alleviated.⁶⁶ Sedation refers to both a subjective sensation of drowsiness and objective measures of psychomotor impairment. According to the Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis,⁵

"Sedation and performance impairment are undesirable and potentially dangerous side effects of first generation antihistamines. Studies have demon-

Figure 6
Change From Baseline in Nasal Symptom Scores of Patients With Seasonal AR Treated Once Daily for 2 Weeks With Placebo, an Antihistamine, or a Leukotriene Modifier



Malmstrom K et al. *J Allergy Clin Immunol.* 2001;107:S157.

strated that many patients may not perceive performance impairment that is associated with these agents. First generation antihistamines have been implicated as causal factors in fatal automobile accidents, confer higher risk for occupational accidents than that associated with narcotics and sedative hypnotics, decrease work performance and productivity, and impair children's learning and academic performance. In the majority of states, patients taking sedating antihistamines are legally considered 'under the influence of drugs.'...Consequently, second generation antihistamines that are associated with less risk or no risk for these side effects should usually be considered before sedating antihistamines for treatment of allergic rhinitis."

Unlike the first-generation antihistamines, second-generation agents cause little or no psychomotor impairment at recommended doses (Table 4). Among many examples of the difference between classes is a randomized, double-blind study in which 98 healthy subjects underwent a battery

Table 4
Key Characteristics of Commonly Used First- and Second-Generation Antihistamines

Agent	Common Adult Daily Dose	Relative Drowsiness Effect	Relative Anticholinergic Effect	Relative Effect on Impairment
First generation				
Diphenhydramine	25-50 mg q4-6h	+++	+++	+++
Chlorpheniramine	4 mg q4-6h	++	+++	++
Brompheniramine	4 mg q6h	++	+++	++
Clemastine	1-2 mg of base TID	+++	+++	+++
Second generation				
Loratadine	10 mg QD	0 (+ at high doses)	+	0 (+ at high doses)
Cetirizine	5-10 mg QD	± (+ at high doses)	+	± (+ at high doses)
Fexofenadine	180 mg QD or 60 mg BID	0	0	0
Desloratadine	5 mg QD	0 (+ at high doses)	+	0 (+ at high doses)

+++ = high effect; ++ = moderate effect; + = low effect; 0 = no effect; ± = low to no effect.

Adapted from *J Allergy Clin Immunol.*, Vol 111, Casale TB et al. First do no harm: Managing antihistamine impairment in patients with allergic rhinitis, pages S835-S842, Copyright 2003, with permission from the American Academy of Allergy, Asthma, and Immunology.

of psychometric tests after taking diphenhydramine (a first-generation drug), loratadine (a second-generation drug), or placebo. The diphenhydramine group exhibited significantly poorer performance than the loratadine or placebo groups on tests of divided attention, working memory, speed, and vigilance. They also reported more fatigue and sleepiness and less motivation, whereas loratadine was not significantly different from placebo on any measure (Figure 7).⁷⁸

In other studies, comparable differences between first- and second-generation antihistamines have been observed in effects on classroom performance, driving ability, work productivity, and workplace injuries.⁷⁹⁻⁸¹ One study, however, found no differences between placebo, diphenhydramine, and loratadine in children's learning ability, reaction time, or somnolence after short-term administration.⁸²

Since their introduction, several early second-generation agents, including terfenadine and astemizole, were withdrawn from the US market because of significant cardiac toxicity.⁶⁶ There may even be some differences between second-generation agents in their potential to

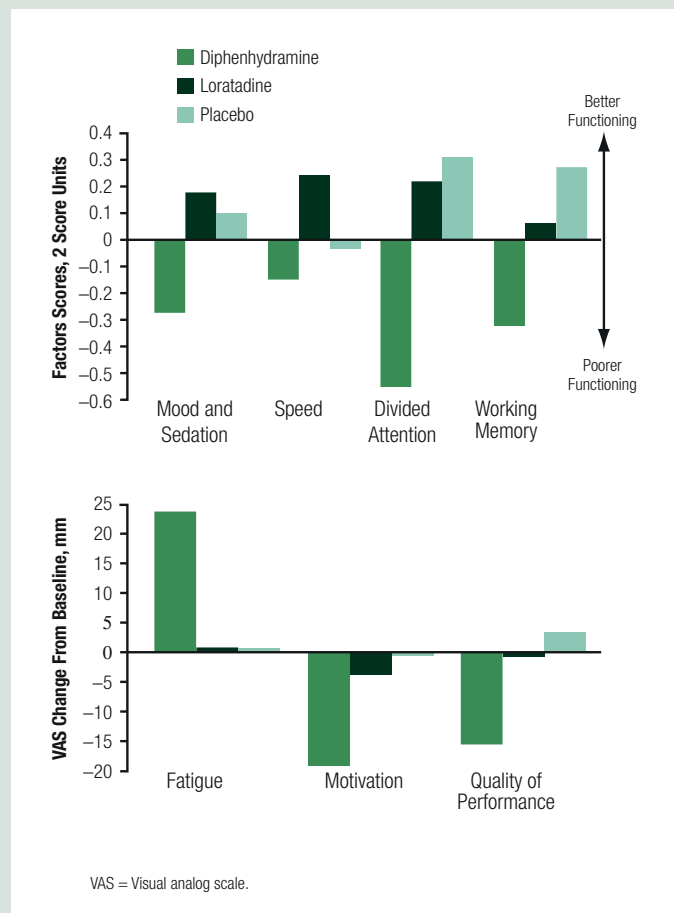
cause sedation, depending on dose (Table 4, page 10). For example, some may cause sedation at standard or higher-than-standard doses,^{65,66} such as those used by patients with refractory AR or urticaria. Overuse of antihistamines sold without prescriptions is a common problem caused by patient misperceptions that they are uniformly safe and that higher doses may be more effective. In reality, higher-than-recommended doses can result in sedation or cardiotoxicity with first-generation antihistamines and some second-generation antihistamines.⁶⁶ In objective tests, only fexofenadine and ebastine have been shown to be virtually without sedative or performance-impairing effects, regardless of dose.⁶⁷ In a review of 76 studies of antihistamine-related sedation in healthy volunteers, each drug was assigned a numerical value based on objective and subjective reports of impairment relative to other antihistamines. A value of zero represented no evidence of impairment across a range of doses, and higher values indicated greater impairments. The value for fexofenadine was 0.00, and that for loratadine was 0.48. By comparison, the values for typical first-generation agents such as chlorpheniramine, diphenhydramine, and promethazine ranged from 1.90 to 2.88. The authors concluded that there are not only differences between the 2 classes of antihistamines in terms of their sedating effects but also differences within the class of second-generation agents.⁸³

Corticosteroids

The chief safety concern with corticosteroids is the risk of systemic side effects such as cataracts and suppression of the hypothalamic-pituitary-adrenal axis. Historically, these were observed with oral steroids; they became less of a concern with the introduction of inhaled agents and with expert recommendations to reserve oral steroids for severe, intractable cases, using only short-acting agents, low doses, and short treatment durations.¹⁵ One of the few remaining safety issues is the potential for steroids to slow the growth of children. Although none of the topical products has a dramatic effect on growth velocity, there may be some modest differences within the class. For example, a year-long study of 98 children with perennial AR showed that mometasone 100 mcg/day had no effect on growth,⁸⁴ whereas a separate year-long study of 100 children found that beclomethasone 336 mcg/day significantly slowed growth compared with placebo.⁸⁵ Two-week courses of intranasal triamcinolone or fluticasone had no effect on lower-leg growth in a recent study using knemometry, which is a highly sensitive measure of short-term changes in the distance between the knee and the heel.⁸⁶

Well-controlled trials have indicated that intranasal steroids are comparable in terms of efficacy, and all are safe^{63,87,88}; the distinction between them is primarily one of patient preference for certain sensory attributes (including overall comfort, burning, run-off, taste, and odor). Since patient preference may influence adherence, this aspect should be considered in prescribing.⁸⁹ Methods for minimizing steroid load include allergen avoidance, titrating use by site (ie, adjusting the inhaled versus the intranasal dose), titrating to the lowest effective dose once efficacy has been achieved, selecting steroids with low bioavailability and efficacy at low doses, using adjunctive nonsteroid therapy, and instituting immunotherapy.

Figure 7
Change From Baseline in Psychometric Variables After 1 Day of Treatment With Diphenhydramine, Loratadine, or Placebo



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Immunotherapy

The efficacy of immunotherapy in the treatment of AR is variable, and it is even more so in allergic conjunctivitis and allergic asthma. However, it has the potential to offer long-term protection against AR even after injections are discontinued.⁴² Moreover, it may help prevent the development of lower-airway disease. In a recent multicenter study, 205 children with grass and tree allergies were randomized into 2 groups: one received specific allergen immunotherapy for 3 years, and the other served as an open control group. Children in both groups were permitted to use standard AR therapies such as oral and topical antihistamines, a topical mast cell stabilizer, and an intranasal steroid. Immunotherapy offered an incremental benefit over the drug therapy: After 3 years, the likelihood of developing asthma was more than twice as high in the control group as in the immunotherapy group.⁹⁰

FOCUS ON ALLERGIC REACTIONS TO FOODS, DRUGS, INSECT STINGS, AND LATEX

The basic steps in diagnosing and managing allergic reactions to foods, drugs, insect stings, and latex are the same regardless of the suspected allergen (Figure 8). When a patient presents to a primary care physician with a history and physical examination that suggest an allergic reaction, the choice of management is determined by whether the reaction was accompanied by systemic symptoms. If so, the most important objective is to arm the patient against the possibility of a repeat event. This entails fully discussing allergen-avoidance measures, providing the patient with self-injectable epinephrine and education on how and when to use it, and referring the patient to an allergist for further workup. If the reaction was exclusively local, symptomatic treatment may be adequate, although referral to an allergist may still be considered.

The allergist's first steps are a detailed history, physical examination, and review of medical records, after which skin testing, serologic testing, and/or allergen challenge may be performed. Once the culprit allergens have been positively identified, long-term management relies on drug therapy to treat future reactions, treatment of related comorbid disorders such as asthma, and immunotherapy if appropriate. Patient education should focus on the natural history of the disease, how to protect against future exposures, and a written action plan for managing such exposures if they do occur. Patients with life-threatening reactions should be encouraged to purchase ID bracelets, necklaces, or cards so that others will know how to help them in case of repeat events.

At periodic follow-up visits, the healthcare team should ask about accidental exposures since the previous visit and assess any possible changes in allergen sensitivity (using additional skin and laboratory tests if necessary). The written action plan should be reviewed and updated, and newly available therapies should be discussed. It is important to refresh patients' memories regularly about how and why to use their current drug regimens. For example, many forget how to use self-injectable epinephrine correctly, especially if

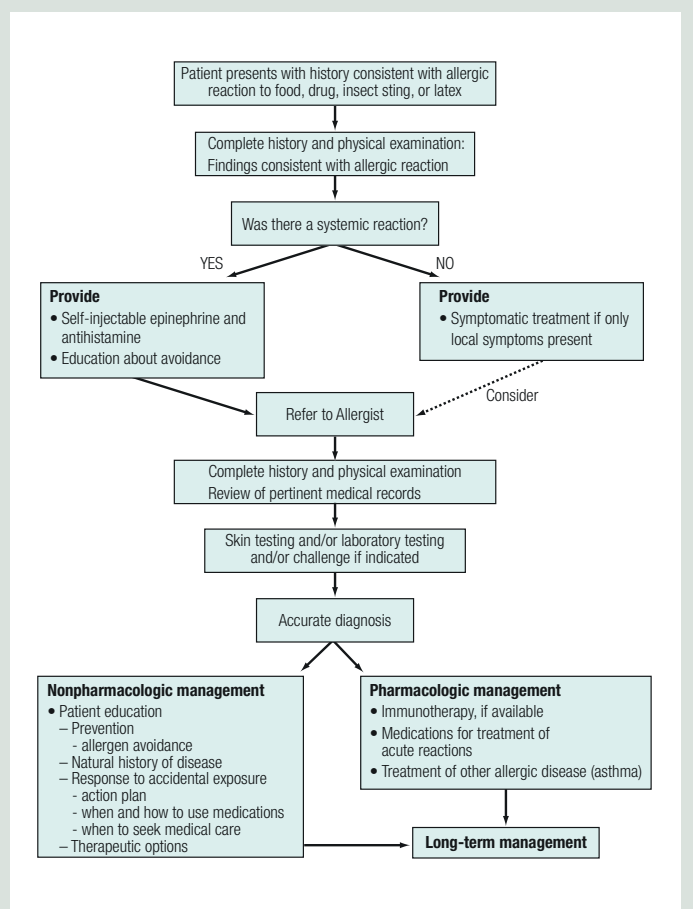
they have not had reactions for some time. Last, the impact of the allergy and its treatment on the patient's emotional health and quality of life should be evaluated.

Food Allergies

Hyperreactivity to foods may be immunologic or nonimmunologic. Although the reactions called "food allergies" are usually IgE mediated, this is not true of all immunologic reactions to foods⁹¹ (eg, celiac disease). Those that are IgE mediated can involve anaphylaxis and are therefore potentially life-threatening. (The exception is oral allergy syndrome, which is a mild, self-limited, localized reaction to certain fresh fruits and vegetables that is often seen in patients with seasonal AR.) In this section, the term "food allergy" refers to IgE-mediated reactions, especially with anaphylaxis. If the history and physical examination suggest a serious IgE-mediated process, skin-prick testing and/or radioallergoimmunosorbent testing (RAST) should be used to assess reactivity to the suspected allergen and other foods that account for the majority of verified reactions (egg, milk, peanuts, soy, fish, tree nuts, and wheat in children and peanuts, tree nuts, fish, and shellfish in adults).⁹¹ Fresh food extracts are often more reliable for skin testing than commercial extracts, especially for fruits and vegetables.

Figure 8

Algorithm for Diagnosing and Managing Allergic Reactions to Foods, Drugs, Insect Stings, or Latex



Most childhood food allergies are outgrown in later life, but allergies to peanuts, tree nuts, and seafood can persist throughout adulthood and are the major causes of life-threatening food allergies.⁹¹

Signs and symptoms of immune-mediated food reactions may occur within minutes to a few hours of ingestion of the offending food; even if symptoms subside, they may recur hours later. Localized manifestations include itching or swelling of the lips, tongue, and oral mucosa; wheeze or cough; nausea or vomiting; abdominal cramps; and diarrhea. Systemic symptoms such as hypotension and shock may occur also, as may urticaria, angioedema, flushing, and other skin symptoms. The reaction may involve upper respiratory symptoms similar to those of AR, including nasal congestion, sneezing, itching, and rhinorrhea.⁹¹

Once the culprit allergens have been identified, an elimination diet and possibly even a food challenge may be used to confirm the association between the food and the patient's symptoms.⁹¹ Future reactions can be minimized with careful avoidance measures, but accidental exposures are not uncommon.⁹¹ Paradoxically, patients who know what they are allergic to may be particularly prone to fatal reactions, because they may mistakenly believe they can avoid the foods even when away from home. In a study of 32 fatal anaphylactic food reactions, 27 of the reactions occurred outside the home. Nearly all the subjects had prior histories of reactions to the foods that caused their deaths, yet only 4 had epinephrine available at the time of the fatal attack.⁹²

Patients should be taught to read food labels and to refrain from eating any food containing unknown ingredients. For allergies to foods that occur widely in the diet or allergies to multiple foods, a dietitian should be consulted to ensure that meals are palatable and nutritious and to help patients recognize food ingredients by unfamiliar names. For example, those allergic to eggs may not realize that they must avoid foods containing albumin, meringue, mayonnaise, globulin, ovovitellin, or lysozyme.

If culprit foods are eaten accidentally, oral antihistamines can be used to manage mild reactions such as localized dermatologic or gastrointestinal symptoms. For the treatment of severe food reactions, epinephrine may be required (see next page, "Management of Anaphylaxis"). Many patients have delayed or biphasic reactions that may be very severe, so they should be monitored for 4 to 6 hours after the initial attack and even longer in cases of anaphylaxis. Extended observation is also advisable after a food challenge. Immunotherapy for food allergy is associated with a high risk of systemic reactions; therefore, it is not recommended.

Drug Allergies

Allergic drug reactions account for approximately 5% of all hospital admissions and occur in up to 20% of hospitalized patients.⁹³ Some are mediated by IgE and manifest as urticaria, anaphylaxis, and severe skin reactions.⁹³

Compounds associated with IgE-mediated drug reactions include penicillins, cephalosporins, sulfonamides, inactive components of certain vaccines, and human proteins such as insulin, vasopressin, corticotropin, and serum/seminal proteins. Other products such as opiates, paralytic agents, vancomycin, fluorescein, dextran, chlorhexidine, and

radiocontrast media can elicit anaphylactic reactions by directly inducing mediator release from mast cells and basophils.

Diagnosis is similar to that of other allergic reactions, with the caveat that false negatives are not uncommon with skin-prick tests for certain drugs. Patients who have experienced allergic drug reactions should memorize the generic and trade names of the offending agents and advise all caregivers of their allergy. For immediate, severe drug reactions, treatment consists of discontinuing the offending agent, administering epinephrine, and prescribing a second-generation antihistamine to help control urticaria, angioedema, and pruritus. Oral corticosteroids may also be indicated. Rechallenge with a suspect drug is absolutely contraindicated in cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, or other life-threatening reactions.⁹³

Insect Venom Allergies

At least 40 deaths are attributable to insect sting reactions each year in the United States, and many more probably go unrecognized. Allergic reactions to insect venom are associated mainly with Hymenopterans such as honeybees, yellow jackets, hornets, wasps, and fire ants. In addition to the typical local sting reactions of redness, swelling, itching, and pain, allergic patients also experience systemic responses. These are chiefly widespread cutaneous symptoms not contiguous with the sting (eg, urticaria and angioedema) but may also include life-threatening symptoms such as bronchospasm, edema of the upper airway, and hypotensive shock.⁹⁴ Any patient who has had a systemic reaction to an insect sting should be advised to carry self-injectable epinephrine and be referred to a specialist for skin and in vitro testing. Prick puncture or intracutaneous skin testing is done with venom (except for fire ants, in which case whole-body extracts are used). Knowing when and where the sting occurred may help identify the responsible insect, which can aid in guiding immunotherapy. However, because accurate identification is rare, skin testing usually includes all the commercially available extracts.⁹⁴

Like airborne allergens, insect stings are difficult to avoid completely. Common-sense measures include hiring professional exterminators; wearing long pants and long-sleeved shirts outdoors; and not wearing brightly colored or flowered clothing, perfume, or hairspray.⁹⁴ When stings occur despite efforts at avoidance, the stinger should be removed by flicking or scraping as soon after the sting as possible. Application of cold compresses and administration of analgesics for pain may be all that is required for an immediate local reaction; oral antihistamines may also be useful for relieving the pain and itching associated with cutaneous reactions.⁹⁴ Topical or oral corticosteroids may be used for especially severe local symptoms, but their use is controversial.⁹⁴ Corticosteroids may also be used to prevent late- or second-phase anaphylaxis. Management of anaphylaxis is summarized on the next page.^{95,96}

Venom immunotherapy (VIT) is very effective for individuals at risk for anaphylaxis, preventing further systemic reactions 97% of the time. It is indicated for patients who have had systemic reactions to stings and in whom IgE sensitivity to the venom can be demonstrated by skin testing or RAST. Exclusively local reactions, even if large, are not generally

Management of Anaphylaxis

Anaphylaxis is an acute, life-threatening immunologic reaction triggered by the release of inflammatory mediators from mast cells and basophils. The most common symptoms are urticaria and angioedema, but there are often other respiratory, cardiovascular, and gastrointestinal manifestations as well, including potentially lethal laryngeal edema, bronchospasm, tachycardia, and hypotension. Symptoms usually develop within minutes of allergen exposure, but late-phase or biphasic reactions may also be observed 8 to 12 hours after the initial attack.¹⁰² Among the allergens most commonly implicated are foods, drugs, venoms, and latex.⁹⁶ Thus, immunotherapy is a potential cause of anaphylaxis and should be given only in a setting where emergency resuscitative equipment and trained personnel are available.

Anaphylactic reactions vary considerably in their severity (Table 5). In all but the mildest cases, management begins with aggressive attention to the ABCs of life support (airway, breathing, and circulation). Intramuscular epinephrine is the mainstay of treatment, and adjunctive measures to maintain oxygenation and circulatory volume are likely to be needed as well (Figure 10).⁹⁶ Epinephrine restores peripheral vasomotor tone, relieves urticaria and angioedema, promotes bronchodilation, enhances myocardial function, and suppresses inflammatory mediator release. Repeat doses and/or intravenous administration may be needed, but excessive amounts carry their own risks and should be avoided. Patients should be monitored for symptom recurrence for 24 hours after initial recovery; recurrent or biphasic anaphylaxis may require twice as much epinephrine as uniphasic symptoms do.⁹⁶

Other treatments to consider include H₁ and H₂ antihistamines, systemic corticosteroids, oxygen, and bronchodilators.^{96,103} Once a patient can be discharged safely, referral to an allergist is mandatory, even if the patient did not suffer shock or cardiac arrest. Patients with coexisting asthma also merit specialist attention, as they have an exceptionally high risk of death from anaphylaxis. In one study, for example, 24 of the 32 fatalities occurred in patients with asthma.⁹² Systemic corticosteroids may also be used to prevent biphasic anaphylaxis.

Patients should be instructed on strategies for avoiding triggers and on how and when to self-administer epinephrine in case of another attack. These messages need to be reinforced regularly, and patients should be encouraged to practice using their self-injectors from time to time. For children with anaphylaxis, education should extend to their parents, school nurses, and other caregivers.

Patients should be strongly encouraged to let themselves be driven to a hospital after an anaphylactic reaction, as the medications they carry with them may not be enough to manage a prolonged or biphasic reaction. This is highlighted by the study mentioned above, in which 4 of the 32 anaphylaxis fatalities occurred despite timely administration of epinephrine.⁹²

Table 5

Grading System for Anaphylaxis

Grade	Clinical Manifestations			
	Skin	Abdomen	Respiratory Tract	Cardiovascular System
I	Pruritus Flushing Urticaria Angioedema			
II	Pruritus	Nausea	Rhinorrhea	Tachycardia (>20 beats/min)
	Flushing	Cramping	Hoarseness	RR change (> 20 mm Hg systolic) [†]
	Urticaria Angioedema (not mandatory)		Dyspnea	Arrhythmia*
III	Pruritus Flushing Urticaria Angioedema (not mandatory)	Vomiting Defecation Diarrhea	Laryngeal edema Bronchospasm Cyanosis	Shock*
IV	Pruritus Flushing Urticaria Angioedema (not mandatory)	Vomiting Defecation Diarrhea	Respiratory arrest	Cardiac arrest

Adapted with permission from Ring J, Behrendt H. *Clin Rev Allergy Immunol*. 1999;17:389.

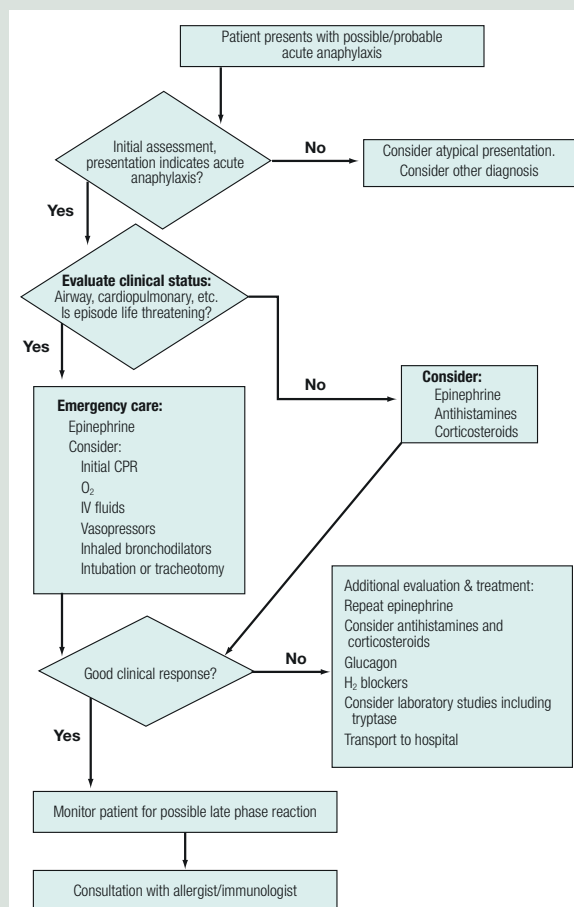
Editors' notes:

*It should be noted that the editors believe that arrhythmia and shock which are noted as Grade II and III respectively are more appropriately considered as Grade III and IV respectively.

[†]Respiratory rate would be more commonly classified as a respiratory tract manifestation as opposed to a cardiovascular system manifestation.

Figure 10

Algorithm for the Management of Anaphylaxis



Adapted from *J Allergy Clin Immunol.*, Vol 101, Nicklas RA. The diagnosis and management of anaphylaxis, pages S465-S528, Copyright 1998, with permission from American Academy of Allergy, Asthma, and Immunology.

indications for immunotherapy. Patients 16 years old or younger who have had cutaneous reactions without other manifestations generally do not need immunotherapy, since they have only a 10% chance of a systemic reaction if resting. Although venom-extract package inserts suggest that therapy be continued indefinitely, patients who have had mild (hives or angioedema limited to the skin) or moderate (mild respiratory symptoms) reactions may discontinue VIT after 3 to 5 years of treatment.⁹⁷

Latex Allergy

The incidence of latex allergy has risen dramatically over the past several years, particularly among healthcare workers and among patients who undergo numerous surgical procedures. The likeliest explanation is the increase in the use of latex gloves: Before the advent of universal blood and body-fluid precautions in 1987, reports of allergic asthmatic reactions to natural rubber latex protein were relatively uncommon, but they became far more frequent in the United States from the late 1980s through the mid-1990s.^{98,99}

Latex exposure and hypersensitivity can occur not only via skin contact with gloves, tourniquets, compression bandages, and other medical devices but also via mucous membranes during the use of condoms, urethral probes, enema kits, etc; via inhalation of aerosolized powder containing latex particles; and via intravascular contact from intravenous (IV) infusion sets. The increased use of latex gloves and condoms may also be related to the fact that latex is superior to other materials in blocking HIV.¹⁰⁰ Additionally, children's products such as toys, balloons, and pacifiers have been associated with hypersensitivity reactions.^{98,99}

The most common reactions to latex are actually nonallergic (irritation) reactions, usually in the form of mild contact dermatitis. A second type of latex reaction, "allergic contact dermatitis," is mediated by T cells and tends to appear hours or days after exposure; most signs and symptoms are confined to the skin. Individuals with this condition can later go on to develop IgE-mediated latex allergy. Allergic contact dermatitis is another example where the term "allergy" is used for non-IgE mediated reactions.

True IgE-mediated latex reactions cause immediate symptoms in the skin (pruritus, urticaria, angioedema), eyes and nose (rhinoconjunctivitis), and lungs (bronchospasm, dyspnea) as well as systemic manifestations such as life-threatening hypotension, tachycardia, and shock. Noncutaneous symptoms are especially common in atopic patients, who constitute a high proportion of latex-sensitized individuals.^{98,99} Patients with latex allergy are at risk for cross-reactivity to avocado, banana, chestnut, and passion fruit, among other foods.^{98,99} The food allergies may precede the latex allergies or vice versa. Diagnosis of latex allergy is based largely on the history and clinical presentation. Skin prick is the most sensitive diagnostic test despite the lack of standardized reagents; in vitro tests are less sensitive, often yielding negative results even in the presence of a clear clinical history.^{98,99}

Because latex allergy has the potential to induce life-threatening anaphylaxis with repeated exposure, avoidance is of the utmost importance. Patients can avoid most

exposures if they are informed and vigilant, but they should be instructed to carry self-injectable epinephrine at all times in case of unanticipated encounters. In healthcare settings, switching from powdered high-protein latex gloves to nonpowdered (or light-powdered) low-protein natural rubber latex gloves may reduce the aerosolized latex protein load, and using gloves made of alternative materials can reduce cutaneous exposure. In a study at a Canadian hospital, the number of healthcare workers identified with latex allergies rose gradually in the early 1990s and then increased sharply when the hospital began education and surveillance efforts. When the hospital switched to low-protein, powder-free latex gloves, the number of diagnoses dropped dramatically (Figure 9), without any increase in glove costs.¹⁰¹ Healthcare workers who know they are atopic should try to protect themselves from sensitization by avoiding natural rubber latex.⁹⁸ Preliminary research has been conducted on immunotherapy for latex allergy, but it cannot be recommended at this point.

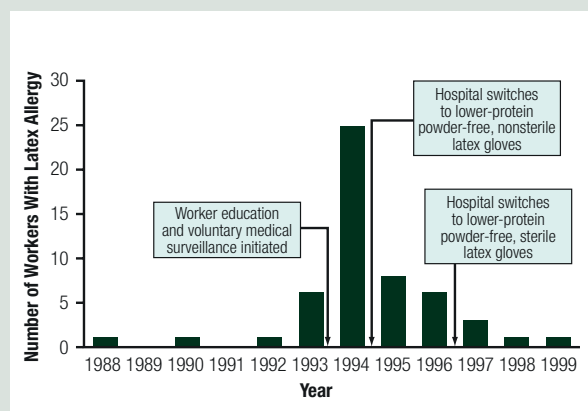
CONDITIONS THAT MAY HAVE ALLERGIC COMPONENTS

Chronic Idiopathic Urticaria

"Urticaria is characterized by the appearance of pruritic, erythematous, cutaneous elevations that blanch with pressure, indicating the presence of dilated blood vessels and edema."¹⁰⁴ Acute urticaria is self-limited and often represents a reaction to foods or drugs. Chronic urticaria is defined as the recurrence of symptoms at least twice weekly for 6 weeks or more.¹⁰⁵ Almost half of patients with chronic urticaria also have angioedema, which consists of painful, prolonged swellings in the deeper dermis, subcutaneous, and submucosal tissues.¹⁰⁶ Like other allergic diseases, chronic urticaria has a profoundly negative impact on quality

Figure 9

Healthcare Workers at a Canadian Hospital Diagnosed With Allergies to Natural Rubber Latex Before and After Interventions to Identify Sensitized Workers and Reduce Exposure



Adapted from *J Allergy Clin Immunol.*, Vol 108, Tarlo SM et al. Outcomes of a natural rubber latex control program in an Ontario teaching hospital, pages 628-633, Copyright 2001, with permission from American Academy of Allergy, Asthma, and Immunology.

of life, being responsible for lost work time; limitations on social activities; disrupted sleep patterns; and feelings of unattractiveness, fatigue, irritability, and weakness.¹⁰⁶

The classification of chronic urticaria/angioedema is summarized in Table 6. Information about the onset and duration of the wheals can be very helpful in pinpointing the diagnosis. Ordinary urticarial lesions resolve within a day, whereas those of urticarial vasculitis usually last several days. Lesions that appear within minutes of trigger exposure and last less than an hour usually signal physical urticaria (except delayed pressure urticaria, in which itchy, painful, or burning lesions emerge several hours after sustained pressure on the skin and last a day or more). Contact urticaria occurs within a half hour of exposure and resolves within 1 to 2 hours (though there may be a delayed phase). One form of physical urticaria often coexists with another or with ordinary urticaria.¹⁰⁵

The release of histamine from mast cells plays a central role in the pathogenesis of wheals and angioedema, and other mast cell products promote and sustain the subsequent inflammatory events.¹⁰⁵ A majority of patients with chronic urticaria have IgG autoimmune antibodies, especially to the high-affinity IgE receptor. However, there is no apparent relationship of these antibodies to symptoms. A related phenomenon may be the increased prevalence of thyroid autoimmunity in patients with chronic urticaria. Many cases of chronic urticaria that were once viewed as idiopathic are probably autoimmune in nature.¹⁰⁵

If the cause of chronic urticaria/angioedema can be identified, management focuses on avoiding the triggers and treating any underlying condition. However, in the majority of cases, etiologic factors are never found. All patients should be encouraged to avoid factors that have aggravated their symptoms in the past, such as heat, tight clothing, stress, or alcohol. Drugs that may cause or aggravate chronic urticaria include angiotensin-converting-enzyme inhibitors, aspirin, and other nonsteroidal anti-inflammatory drugs.¹⁰⁵

Nonsedating H₁ antihistamines are the treatment of choice and are generally effective in relieving pruritus and lesions. Patients usually derive the most benefit by taking the drugs regularly rather than sporadically. Severely affected patients may need higher-than-usual doses.¹⁰⁵ A sedating antihistamine can be added at bedtime for patients whose pruritus interferes with sleep, but this may cause sedation and performance impairment the next day because of the compounds' long half-lives.^{5,105} When necessary, H₂ antagonists, doxepin, or leukotriene modifiers can be added (although the role of the latter agents is not yet well defined). Oral steroids may be required for severe exacerbations, but the dosage should be tapered as soon as the symptoms are controlled. Thyroxine may be useful for patients with positive thyroid autoantibodies, even if they are euthyroid.¹⁰⁵

Atopic Dermatitis

Atopic dermatitis is a chronic, relapsing, highly pruritic inflammatory skin disease that typically involves the flexural areas of the knees, elbows, ankles, and neck in adults and the face and outer limbs in children.¹⁸ Onset is usually in the first year of life; although severity often diminishes in late childhood, many patients are left with a predisposition toward skin diseases such as chronic xerosis and

Table 6
Clinical Classification of Urticaria/Angioedema

- Physical urticaria
 - Adrenergic urticaria
 - Aquagenic urticaria
 - Cholinergic urticaria
 - Cold urticaria
 - Delayed pressure urticaria
 - Dermographism
 - Exercise-induced anaphylaxis
 - Localized heat urticaria
 - Solar urticaria
 - Vibratory angioedema
- Contact urticaria (produced by biologic or chemical skin contact)
- Urticarial vasculitis (defined by vasculitis as shown by skin biopsy specimen)
- Angioedema without urticaria
- Ordinary urticaria (recurrent or episodic urticaria not in the categories above)

Adapted from *J Am Acad Dermatol.*, Vol 46, Grattan CE et al. Chronic urticaria, pages 645-657, Copyright 2002, with permission from the American Academy of Dermatology.

occupational hand dermatitis.¹⁰⁷ They are also at high risk of developing AR or asthma in later life.²⁶ Like other atopic diseases, atopic dermatitis has been increasing in prevalence since the 1960s; epidemiologic studies suggest that the prevalence is now about 17% in American children.^{18,107} The intense itching, cutaneous hyperreactivity, excoriations, and secondary infections disrupt sleep, undermine psychosocial adjustment, and severely impair quality of life for both patients and their families.^{26,107}

The acute lesions of atopic dermatitis are erythematous papules exuding serous fluid, typically excoriated because of scratching. Repeated itch/scratch cycles produce the disease's chronic appearance: thick, lichenified plaques and dry, fibrotic papules.²⁶ Although much remains to be learned about the pathophysiology of atopic dermatitis, extensive evidence points to immune dysregulation in the form of a systemic T_H2 response. Levels of T_H2 cytokines, circulating eosinophils, and serum IgE are elevated, as is the spontaneous release of histamine from basophils, whereas the expression of interferon- γ -secreting T_H1 cells is depressed.²⁶

Triggers of atopic dermatitis overlap strongly with those of AR and asthma, including foods such as egg, milk, wheat, soy, and peanuts and aeroallergens such as dust mites, pollens, animal danders, and molds.²⁶ Recent evidence suggests that some cases may represent abnormal responses to bacterial or fungal skin infections. For example, *Staphylococcus aureus* is found in more than 90% of atopic dermatitis lesions, compared with only 5% of skin samples from healthy subjects. Treatment with anti-staphylococcal antibiotics plus topical corticosteroids reduces the severity of

atopic dermatitis, even for patients without evidence of bacterial superinfection. The pathogenesis is thought to involve certain staphylococcal toxins, which act as superantigens to activate T cells and macrophages. In other cases, patients are sensitized to certain fungi and show responses to antifungal therapy. Autoimmune mechanisms may also play a role in some cases.²⁶

Because of the complexity of atopic dermatitis, a multifaceted approach to treatment is usually needed. Strict avoidance of foodborne and airborne allergens can help alleviate symptoms for individuals who are sensitized to them. Patients should also be advised to apply emollients to their skin after soaking baths each day and to avoid exacerbating factors such as irritants, emotional stress, and infections. Topical steroids are considered first-line treatment for controlling skin inflammation, but they should not be used as maintenance therapy because of the risk of side effects such as skin atrophy. Oral antihistamines are recommended for control of pruritus.²⁶

Topical calcineurin inhibitors represent a novel and highly promising approach to treating atopic dermatitis. These nonsteroidal macrolactones interfere with transcription of inflammatory cytokines, inhibit local T cell activation, and may have other mechanisms of action as well.^{26,108} They significantly reduce staphylococcal colonization of skin and control the symptoms of atopic dermatitis, reducing flare-ups and the need for steroid therapy.^{108,109} They are not associated with steroid-type side effects such as skin atrophy.¹⁰⁹ Two members of this class, tacrolimus and pimecrolimus, have been approved for use for patients as young as 2 years of age. Strategies for combination regimens of corticosteroids and calcineurin inhibitors are now being explored.

Relationship of Allergies to Sinusitis and Asthma

A growing body of evidence suggests that rhinitis, sinusitis, and asthma are not distinct conditions but actually different facets of one disorder, described as chronic respiratory inflammation syndrome. Among the many epidemiologic studies supporting this concept is a cross-sectional analysis of more than 6600 adults in which perennial rhinitis increased the odds of having asthma 8-fold among atopic subjects and more than 11-fold among nonatopic subjects.¹¹⁰ The natural history of the connection is suggested by a longitudinal study of 690 college freshmen in which those with AR were 3 times more likely to develop asthma over the subsequent 23 years than were those without AR (10.5% versus 3.6%, $P<.002$).¹¹¹ The correlation between sinusitis and asthma was shown in a study of 69 patients with asthma that found abnormalities on sinus CT scans in 100% of those with severe steroid-dependent asthma and 88% of those with mild to moderate asthma.²⁸

The onset of asthma involves sensitization to dust mites, animal dander, cockroaches, and the mold *Alternaria*. The severity of asthma is strongly correlated with the number of positive skin tests, and sensitized individuals experience asthmatic symptoms after inhaling aeroallergen extracts. Conversely, avoidance of aeroallergens can improve lung function and ameliorate asthma symptoms for sensitized patients.¹ Even purely topical treatment of upper respiratory

symptoms can improve lower respiratory function; nasal corticosteroids, for example, blunt the increases in bronchial responsiveness and chest symptoms that typically occur during allergy season in patients with concomitant AR and asthma.^{112,113}

A number of functional mechanisms have been proposed for the influence of nasal events on outcomes in the lungs and sinuses. One possibility is that nasal congestion forces patients to breathe through their mouths, which eliminates the ability of the nose to filter, warm, and humidify air before it reaches the lungs. Another theory is that inflammatory products draining out of the upper airways are deposited in the lungs via aspiration. A third possibility is a neural pathway connecting the upper and lower respiratory tracts via the central nervous system such that stimulation of the nasopharynx results in reflex bronchoconstriction. Finally, recent evidence suggests that inflammation in the upper airways may be extended to the lower airways via the systemic circulation.

The Role of Histamine in Airway Inflammation

The fundamental place of histamine in the inflammatory pathophysiology of allergic reactions is well established. In fact, it is implicated in virtually every AR symptom (Table 7). Several lines of evidence now suggest that many inflammatory processes in the asthmatic airway are also mediated by histamine. First, airway levels of histamine are elevated during exacerbations, and the amount of histamine in bronchoalveolar fluid is proportional to the severity of asthma and bronchial hyperreactivity. Second, biopsy investigations show that asthmatic airways contain increased numbers of degranulated mast cells and basophils, and in vitro studies confirm that these cells release unusually high amounts of histamine. Third, histamine is known to elicit many of the pathologic processes that underlie asthma symptoms, including vasodilation, smooth muscle contraction, mucus hypersecretion, and edema.

The fourth piece of evidence is the clinical benefit of antihistamines for patients with asthma. Although they have minimal bronchodilatory effects, antihistamines do decrease airway hyperresponsiveness and help control the symptoms of seasonal asthma. In the Early Treatment of the Atopic Child (ETAC) study, children 1 to 2 years of age with atopic dermatitis were treated with cetirizine or placebo for 18 months. Treatment was then discontinued and the children were followed for an additional 18 months. Although there was no overall beneficial effect shown in this study, it is intriguing that a subset of children who were allergic to house dust mites, grass pollen, or both did experience a beneficial effect to delay or prevent asthma.¹¹⁴ This initial study suggests that second-generation antihistamines may have the potential to delay or prevent asthma onset in some high-risk allergic children.

The epidemiologic and functional relationships between the allergic respiratory diseases shed light on their natural history and pathophysiology and help inform the design of a comprehensive treatment plan. Because allergies coexist with asthma so frequently and because treatment has important benefits for both, it is particularly important to evaluate all patients with asthma for allergic disease.

Table 7

Common Symptoms of Allergic Rhinitis and Their Mediators

Symptoms	Mediators				
	Histamine	Prostaglandins	Leukotrienes	Bradykinin	PAF
Tickling	X	X			
Itching	X	X			
Nose rubbing	X	X			
Allergic "salute"	X	X			
Sneezing	X		X		
Nasal congestion	X		X	X	X
Stuffy nose	X		X	X	X
Mouth breathing	X		X	X	X
Snoring	X		X	X	X
Runny nose	X		X		
Postnasal drip	X		X		
Throat clearing	X		X		

PAF = platelet-activating factor.

Adapted with permission from American Academy of Allergy, Asthma & Immunology. Rhinitis. *The Allergy Report. Volume 2: Diseases of the Atopic Diathesis*. Milwaukee, Wis: AAAAI; 2000:6.

RECENT DEVELOPMENTS IN CARING FOR PATIENTS WITH ALLERGIES

Recent advances in the understanding of immune mechanisms, including mast cell activation, lymphocyte stimulation, inflammatory cell recruitment, and the actions of cytokines and chemokines, are providing new targets for the treatment of allergic diseases. The most promising avenues are those that focus on suppressing or modifying the consequences of T_H2 responses. A prominent example is omalizumab, a humanized monoclonal antibody that binds with and neutralizes circulating IgE, limiting the ability of IgE to trigger the release of inflammatory mediators upon antigen exposure.¹¹⁵ In clinical trials, subcutaneous injections of omalizumab have been shown to decrease symptoms of seasonal AR while reducing the need for other allergy medications, to reduce allergic asthma exacerbations and hospitalizations while decreasing steroid use, and to improve both rhinitis-specific and asthma-specific quality of life.¹¹⁶⁻¹¹⁸ Anti-IgE monoclonal antibodies have also been shown to increase the threshold of sensitivity to peanuts significantly in allergic patients to a level that could protect against some unintended ingestions.¹¹⁹

Investigational Approaches

Other strategies that are now being explored include modulating T_H1 or T_H2 cytokines or their receptors and vaccination with immunoregulatory oligonucleotides. Early evidence suggests that certain sequences from bacterial DNA may be able to stimulate the vertebrate immune system to produce interferon- γ and other cytokines that favor T cell development along T_H1 (nonallergic) pathways.¹²⁰ This may account for the ability of childhood infections to protect against asthma.¹²¹ The DNA segments all contain CpG motifs, which consist of a cytosine and guanine flanked

by 2 purines on one side and 2 pyrimidines on the other. In mouse models, these immunostimulatory sequences (ISS) have been shown to inhibit methacholine responsiveness, diminish the production of IgE and T_H2 cytokines, and prevent allergen-induced airway inflammation.^{120,121}

Because ISS influence T cell differentiation, they could theoretically prevent allergies, not just treat them. However, even if ISS do prove to be safe and effective for prevention, there will be dilemmas regarding which patients will be candidates; at present, there are no genetic markers that reliably identify patients at risk for developing allergies.

SUMMARY/CONCLUSIONS

Allergic diseases affect millions of Americans annually, and their prevalence continues to increase. Although they have a tremendous impact on daily functioning and quality of life and predispose patients to much more serious and costly conditions, they are too often dismissed as nuisance conditions. Even when healthcare providers are committed to treatment, the time constraints of today's clinical practice limit the amount of attention that can be devoted to meticulous analysis of symptoms, repeated adjustments of therapy, and thorough patient education. Fortunately, recent advances in air-filtering technologies and food requirements allow many patients to avoid or reduce allergen exposure in ways they never could before. Newer and more potent drugs and delivery formulations are now available, and additional therapies are in development. With a multidisciplinary approach to prevention and treatment, physicians and allied health professionals can now develop individualized plans that are effective, safe, cost-effective, and acceptable to patients throughout the course of their disease.

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CURRENT TRENDS IN ALLERGIC REACTIONS: A MULTIDISCIPLINARY APPROACH TO PATIENT MANAGEMENT

CME Credit Information and Posttest Assessment

Release Date: September 2003

Expiration Date: September 2004

PHYSICIANS

This activity has been jointly planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of National Jewish Medical and Research Center and IMED Communications. National Jewish Medical and Research Center is accredited by the ACCME to provide continuing medical education for physicians.

National Jewish Medical and Research Center designates this educational activity for up to 2 category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

INSTRUCTIONS:

To apply for category 1 credit, you must:

- Complete the posttest and evaluation form
- Mail your completed form to

Office of Professional Education
National Jewish Medical and Research Center
1400 Jackson Street
Room G107
Denver, CO 80206 **Or** fax to 1-866-384-4335

NURSES AND NURSE PRACTITIONERS

National Jewish Medical and Research Center is Provider approved by the California board of Registered Nursing, Provider Number CEP 12724, for 2.0 contact hours.

INSTRUCTIONS:

To apply for contact hours, you must:

- Complete the posttest and evaluation form
- Fax to our toll free number 1-866-384-4335

National Jewish Medical and Research Center
1400 Jackson Street
Room M-319
Denver, CO 80206

PHYSICIAN ASSISTANTS

This program has been reviewed and is approved for 2 hours of clinical Category I (Preapproved) CME credit by the Physician Assistant Review Panel. Approval is valid for 1 year from the issue date of September 2003. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

Successful completion of the self-assessment is required to earn Category I (Preapproved) CME credit. Successful completion is defined as a cumulative score of at least 70% correct.

INSTRUCTIONS:

To receive CME credit, Physician Assistants should submit this posttest online. You will get immediate feedback and can print your certificate of completion right away. (70% correct required for credit.) Sign onto the AAPA website at www.aapa.org and go to the CME services section. Click on the link to "Post-Tests Online."

POSTTEST

- Allergy to avocado often coexists with allergy to
 - a. Latex
 - b. Fire ant venom
 - c. Peanut
 - d. Birch pollen
- Which of the following is NOT recommended as a component of emergency treatment for food allergies?
 - a. Epinephrine
 - b. H₁ and H₂ antihistamines
 - c. Systemic corticosteroids
 - d. Immunotherapy
- Triggers of atopic dermatitis may include all of the following foods except:
 - a. Egg
 - b. Milk
 - c. Peanut
 - d. Gluten
- In most cases of chronic urticaria/angioedema, the culprit allergens can be identified by
 - a. The history and physical examination
 - b. Skin prick testing
 - c. Serologic testing
 - d. None of the above
- Which condition is associated with a particularly high risk of death during an anaphylactic reaction?
 - a. Atopic dermatitis
 - b. Asthma
 - c. Sinusitis
 - d. Acute gastritis
- Compared with early-phase allergic reactions, late-phase reactions tend to be
 - a. More severe but shorter
 - b. Less severe and shorter
 - c. More severe and prolonged
 - d. Less severe but prolonged
- Omalizumab is a monoclonal antibody that interrupts the allergic inflammatory cascade by binding to
 - a. Histamine
 - b. Eosinophils
 - c. IgE
 - d. Cysteinyl leukotrienes
- A major and often underestimated side effect of intranasal decongestants is
 - a. Atopic dermatitis
 - b. Urticaria
 - c. Rhinitis medicamentosa
 - d. None of the above
- Allergic contact dermatitis is mediated by:
 - a. IgE-producing cells
 - b. IgG-producing cells
 - c. T cells
 - d. Autoantibodies
- The majority of patients with allergic rhinitis also suffer from
 - a. Conjunctivitis
 - b. Otitis media
 - c. Sinusitis
 - d. All of the above

1. a; 2. d; 3. d; 4. d; 5. b; 6. c; 7. c; 8. c; 9. c; 10. d
ANSWER KEY



25231

CURRENT TRENDS IN ALLERGIC REACTIONS:
A Multidisciplinary Approach to Patient Management Monograph
Continuing Education Post Test

- | | |
|--|---|
| 1. <input type="radio"/> a. <input type="radio"/> b. <input type="radio"/> c. <input type="radio"/> d. | 6. <input type="radio"/> a. <input type="radio"/> b. <input type="radio"/> c. <input type="radio"/> d. |
| 2. <input type="radio"/> a. <input type="radio"/> b. <input type="radio"/> c. <input type="radio"/> d. | 7. <input type="radio"/> a. <input type="radio"/> b. <input type="radio"/> c. <input type="radio"/> d. |
| 3. <input type="radio"/> a. <input type="radio"/> b. <input type="radio"/> c. <input type="radio"/> d. | 8. <input type="radio"/> a. <input type="radio"/> b. <input type="radio"/> c. <input type="radio"/> d. |
| 4. <input type="radio"/> a. <input type="radio"/> b. <input type="radio"/> c. <input type="radio"/> d. | 9. <input type="radio"/> a. <input type="radio"/> b. <input type="radio"/> c. <input type="radio"/> d. |
| 5. <input type="radio"/> a. <input type="radio"/> b. <input type="radio"/> c. <input type="radio"/> d. | 10. <input type="radio"/> a. <input type="radio"/> b. <input type="radio"/> c. <input type="radio"/> d. |

Program Evaluation

Your frank evaluation of this activity will be helpful in improving our continuing education programs. We hope this monograph has provided information that will be useful in your practice. Please evaluate the monograph by answering the following questions.

- | | Superior | Excellent | Good | Fair | Poor |
|--|-----------------------|-----------------------|-----------------------|---------------------------|--------------------------|
| 1. How would you rate: | | | | | |
| a. Value of the topic | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| b. Relevance to your practice | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| c. Quality of information | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 2. Did this material succeed in meeting its educational objectives? | | | | <input type="radio"/> Yes | <input type="radio"/> No |
| 3. Will reading this monograph change the way in which you treat patients? | | | | <input type="radio"/> Yes | <input type="radio"/> No |
| 4. Do you believe the monograph contained pharmaceutical industry bias? | | | | <input type="radio"/> Yes | <input type="radio"/> No |
| 5. When information is presented by a federal healthcare agency (i.e. NIH, DHHS, CDC) does it increase the likelihood that you will read it? | | | | | |
| <input type="radio"/> Yes, definitely <input type="radio"/> Neutral <input type="radio"/> No, no change | | | | | |
| 6. How do you prefer to receive continuing medical education information? | Very Useful | Somewhat Useful | Don't Use | | |
| a. Newsletter | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | |
| b. Monograph | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | |
| c. Symposium/Conference | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | |
| d. Journal Articles | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | |
| e. Teleconference | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | |
| f. CD-ROM/Audio and/or video | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | |
| g. Internet | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | | |

7. Actual amount of time I spent in this activity: . Hours

Last Name																								
First Name																								
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Email																								
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									Date															

To receive your certificate fax this completed sheet to 1-866-384-4335.

For additional continuing medical education opportunities related to this subject, visit the National Institute of Allergy and Infectious Diseases of the National Institutes of Health
Web site at:
<http://www.niaid.nih.gov/research/dait.htm>.

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and Immune Diseases



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